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THE BABINSKI PLANTAR RESPONSE, ITS FORMS AND ITS PHYSIOLOGICAL AND PATHOLOGICAL SIGNIFICANCE

BY

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INTRODUCTION

IT is exactly sixty years since, in a short paper, Babinski (1896) first described the sign which now bears his name. For many years it was accepted simply as a clinical sign pathognomonic of a disorder of function in the pyramidal system, though not always of structural damage to that tract. In the second decade of the present century the attention of neurologists, particularly in France, was attracted to ample movements of reflex flexion of the lower limbs in some cases of spinal cord lesion, and the view was then first expressed (Marie and Foix, 1912) that the Babinski plantar response was an integral part of these limb reflexes. The question then became one of controversy between Babinski and his colleagues, never resolved as far as he was concerned. Nevertheless, since that time it has been widely accepted that the Babinski response is but a component of a wider reflex flexion of the limb.

However, within the last few years the question has been raised again by Hoff and Breckenridge (1956) by Lassek (1954) and by Nathan and Smith (1955), and the moment may be opportune for a review of the subject.

In their paper entitled "Observations on the mammalian prototype of the sign of Babinski" (1956), Hoff and Breckenridge open with the following propositions: "few pathological reflexes are as poorly understood from the neurophysiological standpoint as the sign of Babinski, a reflex which more by tradition than by demonstration is considered as pathognomonic of a lesion of the pyramidal tract." Elsewhere they remark that the generally held view that the sign of Babinski is a nociceptive reflex in man homologous with the flexion-reflex of the spinal animal (Sherrington), is based merely on convention. Thus in a few easy and somewhat contemptuous sentences they write off a considerable mass of clinico-pathological knowledge as having no scientific substance.

In so far as their opening sentence refers to their own situation, few readers would be disposed to dispute its accuracy, but if the authors assume, as seems to be the case, that their own poverty of understanding

is widely shared, then I must respectfully submit that they are in error. There is an impressive body of generally accepted data to support the opinions they reject.

They further maintain that Fulton based his analysis of the sign of Babinski upon the present writer's paper on this subject in 1914. It is not clear on what they base this view, for in that analysis Fulton and Keller (1932) neither mention the paper in their text nor quote from it. On the contrary, they make the explicit claim (p. 10) that "no previous investigator has attempted a physiological analysis of the Babinski phenomenon."

A problem arises here, for both Fulton and Keller, and now Hoff and Breckenridge, on the strength of animal experiments only, are claiming to give a reasoned elucidation of the form and nature of a phenomenon discovered and described in the human subject by Babinski, and later given (Walshe, 1914) an interpretation which Hoff and Breckenridge reject.

How can animal experiments be used either to confirm or to controvert factual data and conclusions derived therefrom in the human subject? Clearly, these stand upon their own foundations, and can be confirmed or rejected only on the basis of further clinical observations on the human subject.

Sir James Paget, who coined the term "clinical science," said of it that "within our range of study that alone is true which is proved clinically, and that which is clinically proved needs no other evidence." If a series of clinical observations is found to be soundly based, and the conclusions drawn from them are seen to flow naturally from them, a failure to obtain similar observations in cat, dog, or monkey, leaves their validity untouched. Conversely, the obtaining of data in animals identical with those found in man in similar circumstances does not lend confirmation to the clinical observations, it merely establishes an homology, and the establishment of an homology between the phenomena of clinical observation in man and of those of experiment in animals rests upon an accurate knowledge of both so that their resemblances, and their differences if any, may be evaluated.

To give an accurate account of the sign of Babinski and its associated reflex phenomena, and to establish an homology between it and the nociceptive flexion-reflex of Sherrington were two of the objects of the paper entitled "The physiological significance of the reflex phenomena in spastic paralysis of the lower limbs" (Walshe, 1914).

Babinski's Original Description of His Sign, and His Subsequent Views as to Its Independence of the Flexion-reflex of the Limb

A fundamental criticism of Hoff and Breckenridge's paper is that they have not fully acquainted themselves with the literature of their subject, and that, when they refer to this, they do so incompletely and even inaccurately.

This is the case in connexion with Babinski's various pronouncements upon the sign that bears his name. For example, they have not given the reader his original description of this sign. It is essential that this should be recalled. Babinski gave his description in two papers (1896, 1898). In the first, speaking of the occurrence of the sign in cases of hemiplegia, he writes as follows : "Du côté sain, la piqûre de la plante du pied provoque, comme cela a lieu d'habitude à l'état normal, une flexion de la cuisse sur le bassin, de la jambe sur la cuisse, du pied sur la jambe et des orteils sur le métatarse. Du côté paralysé, une excitation semblable donne lieu aussi à une flexion de la cuisse sur le bassin, de la jambe sur la cuisse, et du pied sur la jambe, mais les orteils, au lieu de se fléchir, exécutent un mouvement d'extension sur la métatarse."

Here we have in his own words the classic description of the sign of Babinski, as he first saw it, consisting of dorsiflexion of toes and ankle with flexion at knee and hip, and evoked by a nociceptive stimulus.

It is interesting to compare this clear and concise description with Hoff and Breckenridge's comment. Thus, they state, "Against this conventional identification of the Babinski response with the nociceptive flexor response [*sic*] has always stood the independent opinion of Babinski himself, who from the time of his earliest studies upon the sign rejected the simple view that the response which received his name was but a part of a general flexion-reflex."

This statement is a pure flight of imagination, for Babinski first expressed the view here attributed to him some sixteen years later in 1912. In 1896, no one was discussing flexion-reflexes in man, and indeed even Sherrington had not yet got round to them in animals. Only the first glimmerings of his later discoveries on this reflex appear in his Croonian lectures of 1898, and the first comprehensive account of the flexion-reflex appeared in 1906 in "The Integrative Action of the Nervous System."

Nevertheless, while we may not dispute that what Babinski described had all the characters of a nociceptive flexion-reflex, yet at the moment of its discovery all that concerned him and his neurological colleagues was the "phénomène des orteils"; the upgoing hallux. It was this that was *clinically* important, once its relation to disordered function of the pyramidal tract became apparent. It was to the latter problem that Babinski proceeded to turn his attention, and concerned himself not at all with flexion-reflexes.

In his second paper (1898) Babinski says, "Le phénomène des orteils peut se présenter sous des formes frustes, c'est à dire que le réflexe plantaire peut revêtir des caractères en partie pathologiques, en partie physiologiques. En voici des examples: chez certains sujets, l'excitation de la plante du pied ne provoque d'extension que dans le gros orteil ou dans les deux premiers orteils et donne lieu au même temps à une flexion des

derniers orteils; chez d'autres, les orteils s'étendent quand on excite la partie externe de la plante du pied et se fléchissent lorsque c'est la partie interne du pied qui est excitée; chez d'autres encore, le réflexe plantaire, quelle que soit la partie de la plante du pied qui est excitée, se manifeste tantôt par de la flexion, tantôt par de l'extension des orteils; dans ce dernier cas, ce sont généralement les premières excitations qui donnent lieu à de la flexion."

In 1900, he described reflex dorsiflexion of foot and toes upon pinching either the tendo achillis (Schaefer's reflex) or merely the skin over the tendon in the paralysed limb of hemiplegics. In 1903, he added abduction or fanning of the toes to the dorsiflexion of his "phénomène des orteils," but not as a constant component.

It was in the period from 1910 to 1915 that the occurrence of reflex flexion movements in the lower limbs first attracted the attention of French neurologists (Marie and Foix, 1912) and these became known variously as "réflexes de défense," "réflexes d'automatisme médullaires," and "phénomène des raccourcisseurs."

These reflex "triple flexion movements" absorbed the "phénomène des orteils" in the sense that this came to be regarded by Marie and Foix and others as but a component in the larger reaction. At this juncture for the first time, Babinski expressed the view that the flexion at hip and knee that he had mentioned in his original account of his sign was something different in significance and nature from his "phénomène des orteils."

The perusal of his three papers (1912, 1915, 1922) shows the progressive hardening of his opinion on this point, though the grounds for the objection remain the same throughout, namely, that occasionally reflex limb flexion is found without an associated "phénomène des orteils". His first reference is contained in a footnote (1912) where he says, "en se plaçant au point de vue de la clinique, je crois qu'il est préférable de dissocier ces deux phénomènes," and he goes on to cite the case reported by Dejerine and Levy-Valensi (1911) and Dejerine and Long (1912). Later (1915) he cites an additional case reported by Pastine (1913). Both cases afford scant support for his thesis, but since they have been incompletely exhumed from the literature by Hoff and Breckenridge and by Nathan and Smith (1955), they must be considered.

(1) *The case of Dejerine and Levy-Valensi and Dejerine and Long.*—The patient was a young acrobat who while on tour in the United States fell from the top of a human pyramid sustaining an immediate quadriplegia. Six months later he reached the Salpétrière where his condition on admission is recorded as follows: (lower limbs only described here). There were bedsores on sacrum and heels. There was total flaccid palsy of both lower limbs with wasting. The tendon-jerks were absent, the plantar responses flexor. The record goes on as follows: "les pieds sont en varus-equin et les orteils en flexion. *Cette déformation est aujourd'hui fixée par des retractions fibro-musculaires.*"[1] On forcible flexion of the toes by the observer the limb went into powerful reflex-flexion.

[1] Italics not in original.

The patient died six months after admission to the Salpétrière, i.e. over 11 months after his injury (not ten weeks as Nathan and Smith aver), and at autopsy Dejerine and Long found a fracture-dislocation of the sixth cervical vertebra, the spinal cord at this level being reduced to "a thin transparent membrane," and the pyramidal tracts were degenerated.

In the discussion following the presentation of this pathological specimen, Dejerine stated that during the six months of the patient's survival in the Salpétrière, the plantar responses were consistently in flexion. From this Dejerine drew the conclusion that the sign of Babinski cannot be the result solely of pyramidal tract lesions. He made no reference to the fixed deformity of the feet and toes in plantar flexion, which made impossible the development of a sign of Babinski upon appropriate stimulation, though in the course of the discussion Pierre Marie drew his attention to it as a factor invalidating his conclusion.

In his silence upon this point, Dejerine has now been followed by Hoff and Breckenridge and also by Nathan and Smith, although the objection was again fully discussed by the present writer in his paper of 1914.

Babinski himself was more forthcoming and did not evade this issue, but suggested (1922) that probably before fixation set in the plantar responses were still in plantar flexion. The records in the paper of Dejerine and Levy-Valensi give no grounds for such a speculation.

(2) *The case of Pastine* (1913).—This was one of spastic paraplegia in extension with limb and ankle clonus. Stimulation of the lateral part of the sole constantly evoked a Babinski plantar response, but stronger stimuli applied proximally: e.g. pinching of dorsum of foot or of calf, or forcible flexion of the toes evoked a hallux movement sometimes in dorsiflexion and sometimes in plantar flexion. The exact wording is, "tout les orteils se fléchissent vivement, je le répète, mais pas toujours: quelquefois, d'un seul côté ou de deux côtés, les gros orteils se portent en extension."

This case is advanced to establish the independence of the sign of Babinski from the flexion-reflex. All it shows is that unusual variability of hallux response that in 1898 Babinski was describing as a "forme fruste" of his sign.

Indeed, in his attitude on this matter Babinski was not consistent, for as late as 1922 in answer to Marie and Foix, he said as follows: "Je suis très porté a admettre que la pathogénie du signe des orteils ressemble à celle de la triple flexion . . . Je n'ai pas pretendu qu'il y eut différence absolue de nature entre le signs des orteils et les réflexes cutanés de défense." Nevertheless, although giving away his thesis by this admission, in his several papers upon the extended and flexed forms of paraplegia he described the sign of Babinski and the "réflexes de défense" separately as though they were unrelated.

It is difficult to escape the surmise that a paternal feeling for a sign by which he had so enriched clinical neurology made him reluctant to see it

merged in a larger reflex reaction, lose its individuality and perhaps even its name. The lecture of 1922 does reveal the difficulty he had in finding cogent grounds for separating his sign from reflex flexion of the limb.

Against what it is reasonable to speak of as these negligible objections to the identity of the sign of Babinski with the flexion-reflex of limb, there have to be set, as well as my paper of 1914, the studies of Head and Riddoch (1917), of Riddoch (1917, of Kuhn (1950) and the electromyographic studies of Kugelberg (1948) and Ashby's paper (1949).

In addition, the *Revue Neurologique* during the years 1912 to 1920 contains numerous papers, notably those of Marie and Foix, which, even if the latter authors were in error in identifying the flexion-reflex with reflex stepping, did accept *as a fact of observation* the unity of limb flexion and hallux dorsiflexion in a single reaction. All this weight of observation we are now invited to regard as a mere convention.

An apology may seem necessary for the several and lengthy quotations from the original French, but it will be already clear to the reader, and will become more so, how necessary this has been in view of the often unsatisfactory manner in which the relevant literature is referred to by modern writers on the subject.[1]

The Flexion-Reflex and the Babinski Plantar Response in Man

Herewith is a summary of the observations recorded by me (1914), together with references to more recent clinical studies, particularly those of Kugelberg (1948), Kuhn (1950) and Marshall (1954).

The view originally expressed by me was that the Babinski plantar response ("extensor plantar response" of English writers) is an integral component of a flexion-reflex of the lower limb in which the flexors of the limb and the dorsiflexors of foot and toes all take part. In what follows, the term "flexion reflex" includes the Babinski plantar response, and the latter term is to be understood as referring to a component of this reflex.

(*a*) *The receptive field.*—When minimal this is restricted to the lateral

[1]In writings on the plantar responses and on the flexion and other limb reflexes, no less than three distinct terminologies are in use. (1) *The morphologist's*, in which dorsiflexor muscles are named extensors, and plantar-flexor muscles are named flexors. (2) *The physiologist's* in which the flexion-reflex (Sherrington) is a reaction employing limb flexors and dorsiflexors, while the crossed "extension-reflex" and the "extensor thrust" employ their antagonists, namely the limb extensors and the plantar flexors. (3) *The clinical neurologist's*, in which the normal plantar response is known as the "flexor response," and the Babinski plantar response, employing dorsiflexors, is known as the "extensor response."

The possibilities of confusion here are almost limitless, and all of them seem to be availed of in the literature, where all three terminologies are used, sometimes with no indication as to the precise reference each has; thus, the "flexor response" is sometimes the physiologist's flexion-reflex and sometimes the very different "flexor response" of the clinician.

Thus, the reader cannot always be sure what the writer is referring to.

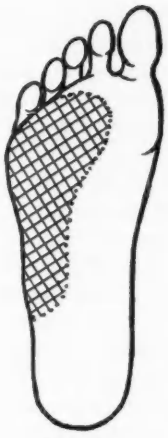

FIG. 1.

part of the sole (fig. 1), and when maximal it may extend to and include the skin and deep structures of the entire limb and may even spread on to the abdominal wall.

As a rule, when the reflex is fully developed, the field rarely reaches higher than the border between the upper and middle third of the thigh in lesions of the spinal cord, but in lesions within the cerebral hemispheres it rarely rises above the level of the knee and may be even more restricted.

The focus of the field, where the threshold of stimulation is lowest, and from which alone the reflex can be elicited when the damaged cord is in spinal shock, in the coma preceding death, and in cases of a rudimentary development of the reflex, is, as already stated, the lateral margin of the sole.

It is not uncommon, more especially in cases of hemiparesis or mild cord lesions, to be able to elicit the extensor plantar response from the lateral part of the sole, while stimulation of the mesial part evokes the normal or "flexor" plantar response.

Further, even when the field is more extensive than the sole, prolonged and heavy stroking pressure over the mesial part of the sole and overlying abductor hallucis provokes a direct contraction of this muscle with a strong plantar flexion of the hallux, even though the hip and knee flexion components of the flexion-reflex persist. The point is of some importance since Marshall (1954) speaks of producing "an ipsilateral extensor reflex by a very slow, prolonged drag of the stimulator," not specifying what part of the sole was stimulated, or indicating in his myograms the duration of the stimulation or the latency of the response in any of his observations. Babinski (1898) has some apt remarks to make on this subject, "Il n'est

pas indifférent d'exciter légèrement ou énergiquement, de chatouiller simplement ou de piquer la plante du pied. Ce dernier mode d'excitation est nécessaire chez certains sujets pour faire apparaître un mouvement réflexe des orteils; mais, par contre, il donne lieu chez d'autres individus à des mouvements si vifs des divers segments du membre inférieur, qu'il est difficile de les analyser," and he goes on to say that voluntary movements may become superimposed upon the reflex.

The eliciting of the Babinski plantar response, in short, is not the simple procedure it is so commonly thought to be.

(*b*) *The adequate stimulus.*—There is a sense in which this is as variable as the receptive field, in that the facility with which the reflex may be evoked is variable. Variable also is the threshold of stimulation at different parts of the receptive field. Yet in man, as in the experimental animal, the adequate stimulus is one that is potentially nocuous in all save exceptional circumstances to be later mentioned. Light cotton-wool touch is not adequate, and stroking pressure on the sole at least, as every neurologist knows, using a pointed, though not necessarily very sharp, stimulator, or the end of the finger, is required. Proximally in the field more potent stimuli are apt to be necessary: skin pinching, pressure along a muscle (e.g. the technique for eliciting the reflex described by Oppenheim), the application of hot or cold objects, pin-prick, or faradic stimulation. In many cases of paraplegia-in-extension the placing of the cold arm of a tuning-fork upon the mesial surface of the thigh will evoke a complete flexion-reflex response, or one in which the Babinski response is the most ample and evident component.

When the flexion-reflex is extremely powerful, as in a case of paraplegia-in-extension going over into paraplegia-in-flexion, or in an established paraplegia-in-flexion, whether or not voluntary power remains, the reflex is so facile that the lightest stroke or even touch on the sole will fire it off, and, as is well known, drawing the bedclothes off the feet may suffice, while the apparently spontaneous flexor spasms, which are flexion-reflexes, may seem to require no discernible external stimulus.

However, in all but this special situation, the stimulus is characteristically potentially nocuous, i.e. one that by intensification can be made painful or damaging to the tissues, and only cotton-wool touch, which is a single intensity stimulus and essentially innocuous, is inadequate.

The reflex response evoked by these means may properly be described as a nociceptive reflex in Sherrington's sense. This conclusion receives strong confirmation from Kugelberg's electromyographic studies of the reflex in man (1948). He has shown that the reflex is not evoked by stimulation of the large nerve fibres subserving tactile sensory function until the stimulus threshold is so raised as to cause pain, and that the response has two components, an early response to stimulation of A fibres, and a later more powerful response to C fibres. Of these fibres the

former are associated with "first pain" and the latter with "second pain" (cf. Ashby, 1949). To this so significant paper Hoff and Breckenridge make no reference.

(*c*) *The motor reflex response.*—The flexion-reflex in man elicited as described, and also the involuntary flexor spasms of some cases of severe paraplegia (paraplegia-in-extension passing into paraplegia-in-flexion) consist in a flexion movement at hip and knee, and dorsiflexion of foot and hallux, often with dorsiflexion and spreading of the other toes. While the only visible motor response may be dorsiflexion of the hallux, as, for example, in states of depression of the reflex, when it is just evolving, or to minimal stimulation, my experience has been that this visible response is never the sole response, for palpation of semitendinosus behind the knee reveals a contraction of this muscle when there is an extensor response.

According to the facility of the reflex, various degrees of triple flexion of the limb may be seen, slight or extreme, rapid and short-lived in cases of paraplegia-in-extension, slow and sustained in paraplegia-in-flexion. Babinski described his sign as characteristically slow, but this is not invariably the case, for when there is marked extensor hypertonus of the limb the response may be rapid and transitory. Kugelberg's paper contains observations of interest in this connexion.

Although, in my experience, a truly isolated Babinski response does not occur, and even the minimal response involves proximal flexor muscles, the reflex does show some "local sign" as though proximal afferents do not reach the more distal muscles as effectively as they do the proximal muscles, and vice versa. Thus, stimulation of the thigh sometimes tends to produce contraction dominant in proximal flexors, stimulation of the sole contraction dominant in dorsiflexors. Thus, also, at the upper margin of the receptive field, stimulation may yield the variability of toe response originally noted by Babinski, though myographic recording may also reveal a diphasic response from this region (Walshe, 1914, pp. 284–286) in which a brief plantar flexion of the hallux precedes the flexion-reflex which then includes dorsiflexion of the hallux.

Variations in the Flexion-reflex in Man

It would be satisfactory if one could leave the consideration of the flexion-reflex in man at this point, but the experiments of disease in man are rarely so tidy as those of the experimental laboratory, and there are some variations in observation still to be faced. These include (1) the occasional association of limb flexion with foot and toe plantar flexion when the reflex reaction is well-developed in man, and (2) the initial response of hallux plantar flexion that may endure for some days immediately after an acute transverse lesion of the cord leading to the phenomena of spinal shock.

Marie and Foix, although accepting that the Babinski response was an

integral part of reflex-flexion of the limb, yet noted the occasional appearance of the latter without the former, and circumstances in which this separation may be seen have also been recorded here. Recently, Marshall (*loc. cit.*) has returned to this subject in some clinical studies and has described an apparently much more capricious state of the reflexes in the lower limb than has hitherto been noted.

In my own experience, using the modes of stimulation to which I have always been accustomed, and bearing in mind the danger of evoking quasi-voluntary movements when stimulation is painful or unduly prolonged, I have not encountered this extreme variability of response. Thus, "heavy pressure by a very slow, prolonged drag of the stimulator," unless there is loss of pain sense and unless also the skin over abductor hallucis is avoided, must produce results most difficult of interpretation.

However, the greater variety of reflex pattern which, under the conditions of his observations, Marshall describes, does not invalidate the occurrence of a nociceptive flexion-reflex in man of which the Babinski plantar response is an integral part, and is not regarded by him as doing so. The simple methods of studying and analysing reflexes in man that were alone available forty years ago have now been supplanted by such methods as Kugelberg's, and a repetition of Marshall's observations employing better calibrated modes and durations of stimulation and electromyographic recording might yield results less open to fallacy.

However, it seems probable that the explanation of incomplete flexion-reflexes in man must be sought first in such considerations as those advanced by Sherrington (1910), namely that not all the afferents from the very wide receptive field of the flexion-reflex reach every one of the limb flexors, and, perhaps even more important, in considerations fully discussed by Creed, Denny-Brown, Eccles, Liddell and Sherrington ("Reflex Activity of the Spinal Cord," 1932) and summarized by them as follows (p. 107): "Reversal of reflex effect. 'Reversal' is germane to concealed reflexes. It is met with in several forms: (*a*) reversal under change of strength of stimulation of the same afferent nerve; (*b*) reversal under continued and unaltered application of the stimulus; (*c*) reversal after exhibition of a drug, e.g. chloroform, strychnine, the stimulus and nerve remaining the same; (*d*) reversal conditioned by altered initial state, e.g. posture of the limb, the exciting stimulus and its locus being unaltered."

If there be an homology between the flexion-reflex in man and that described by Sherrington in the experimental animal, and such is the thesis of this paper, then the conditions governing variability of response in one may be applied to the other. Also, since these variations in the experimentally obtained flexion-reflex do not invalidate Sherrington's original description of this reflex as typically consisting in reflex contraction of all the limb flexors and of the dorsiflexors of foot and digits and the reciprocal inhibition of their antagonists, then they do not invalidate the

view generally taken by clinical neurologists that the Babinski plantar response is an integral part of the flexion-reflex in man.

Flexion-reflex in Total Cord Lesions

We have yet to consider briefly the form of the plantar response that may be obtained after an acute transverse lesion of the spinal cord in man producing the picture of flaccid palsy with tendon areflexia. Head and Riddoch (1917) and Kuhn (1950) and other writers dealing with smaller series of cases have noted that initially there may be no plantar response of any kind to plantar or limb stimulation, and that after a few days—and persisting only for a period of days as a rule—an isolated plantar flexion of the hallux may appear on plantar stimulation. A similar state of affairs is described by Sherrington in the monkey after cord transection and in spinal shock (1898).

My own experience is similar, but I have noted that in some instances the initial areflexia of the sole is followed by the appearance of a minimal flexion-reflex: that is, the Babinski plantar response plus palpable contraction of the inner hamstrings behind the knee, *or the latter alone at first*. I have not seen the plantar-flexion response and the flexion-reflex of the limb overlapping, but this has been noted by other authors. In general, the appearance of the full flexion-reflex in such circumstances is the signal for the early disappearance of the initial plantar flexion response of the hallux.

Here, again, it is probable that only electromyographic studies such as those of Kugelberg will throw light upon this brief initial response and its relations, if any, to the full flexion reflex. Again, however, the occurrence of this toe plantar flexion does not invalidate the generalization already made as to the constitution of the flexion-reflex in man and as to the relation to it of the Babinski plantar response.

Reflexes Accessory to the Flexion-reflex in Man

But all has not yet been said of the flexion-reflex in man, and brief reference is necessary to the accessory reflexes that accompany it frequently though by no means constantly. These are the crossed extension reflex and the reflex rebound.

The crossed extension reflex in the human subject was first noted as a movement of plantar flexion of foot and toes in the contralateral limb upon the eliciting of the Babinski response (Bramwell, 1911; Fairbanks, 1911). It is frequent in cases of paraplegia-in-extension when there is evident hypertonus. If, in such cases, when the flexion-reflex is being evoked, the crossed lower limb is held in flexion by an assistant, the entire limb is seen to extend actively at hip, knee and ankle with plantar flexion of the toes. Further, in some cases, following these reactions, the limbs may show a short active rebound, the stimulated leg extending and the

crossed one executing a flexion-reflex. This state of affairs was fully discussed and illustrated photographically and myographically in my paper of 1914 (Fig. 8, A, B, C, pp. 295–296).

In anticipation of what is to be said in the following chapter, it may here be noted that Sherrington points out that the crossed extension reflex is a reflex accessory to the flexion-reflex *and except as an accessory is not found.* Thus, the presence of this crossed reaction in man points to the homology between the flexion-reflex in man and that in the experimental animal.

We may end this long chapter by saying that the flexion-reflex in man consists of dorsiflexion of foot and toes and of flexion at hip and knee, and is evoked by a nociceptive stimulus.

Thus to define it, is simply to paraphase the terms in which Babinski originally made the equivalent statement about his sign. We cannot but regret that, the facts being unchanged, he altered his mind and much later adopted the idea of a separation between the distal and the proximal elements in his reflex.

Sherrington on the Flexion-reflex

If an homology is to be established between the flexion-reflex in man and the nociceptive flexion-reflex of animals described by Sherrington, the latter must be described. Sherrington gave a most complete analysis and description of this reflex, studying the participating and the antagonist muscles one by one by the myographic method, and using also quantitative stimuli (1910).

It should be scarcely necessary to summarize this account, were it not that Hoff and Breckenridge refer to it incompletely, and incorrectly in some significant respects. Further, Fulton and Keller in their analysis of the homologue of the Babinski response in monkeys and apes used only the method of inspection of the reacting limbs. They thus were unable to confirm or to exclude in the monkey that typical participation of the dorsiflexors of foot and toes that Sherrington observed in his more thorough researches.

It cannot be necessary to repeat what Sherrington records in respect of the receptive field and the adequate stimulus for the flexion-reflex, for these tally so precisely with what has been found in man.

It is necessary, however, to discuss the motor response, for Hoff and Breckenridge say that "when the reflex behaviour of the spinal dog and cat is studied . . . the nociceptive flexor response [*sic*] invariably involves plantar-flexion of the toes."

This statement is in direct conflict with the facts recorded by Sherrington. The muscles found to react in the flexion-reflex include all the limb flexors and the dorsi-flexors of foot and digits. Those which relax include the limb extensors, soleus, gastrocnemius and sometimes flexor longus

digitorum. This last-named muscle does not contract in the flexion-reflex. Lists of the muscles active in the flexion-reflex are given in the paper (1910). They are as follows:

CONTRACTING

Psoas parvus	Pectineus
Ilio-psoas	Gluteus minimus
Tensor fasciæ femoris longus	Tenuissimus
„ „ „ brevis	Biceps femoris (post. part)
Sartorius, medial band	Semitendinosus
„ lateral band (distal)	Tibialis anticus
Rectus femoris	Peroneus longus
Gracilis	Extensor long. digitorum
Adductor magnus (part)	„ brev. „

INHIBITED

Semimembranosus	Adductor magnus (part)
Biceps fem. (ant. part)	Quadratus femoris
Vastus medialis	Gastrocnemius
Crureus	Plantaris
Vastus lateralis	Soleus
	Adductor minor

In explanation of the contraction of muscles sometimes regarded as extensors, he points out that the flexion-reflex does not always treat as entities those so named in anatomical nomenclature, instancing the different action of the two parts of biceps femoris.

Further details of the action of extensor longus digitorum are also important to note. Thus, "If the ankle be free to flex, the knee flexors by means of extensor longus digitorum dorsiflex the ankle but the toes are not extended, or are even flexed by passive pull of flexor longus digitorum. Extensor longus digitorum if the ankle be not free to flex, extends the toes; if ankle be free it can flex ankle and extend toes; it also slightly separates toes" (pp. 43 and 49).

Here we see the imperative necessity of such an individual analysis of musculature activity as Sherrington has carried out.

In this reflex all dorsiflexors contract and plantar-flexors are inhibited, yet in certain circumstances, owing to mechanical factors, a passive plantar flexion of the toes may be caused.

Finally, flexor longus digitorum strongly flexes toes, but neither flexes nor extends ankle.

It is clear here that "extension" of foot and toes effected by extensor longus digitorum is a movement of dorsiflexion, as opposed to the flexion of the toes produced by flexor longus digitorum.

Thus, we see that in the flexion-reflex of spinal and decerebrate cat and dog the dorsiflexors of foot and toes contract, the plantar flexors (soleus, gastrocnemius, plantaris, flexor longus digitorum) relax.

In these circumstances it is impossible to accept the statement (p. 163)

of Hoff and Breckenridge about the flexion-reflex in animals, "the typical mammalian nociceptive flexor response [*sic*] which by its marked toe flexion resembles the normal plantar response of the human foot and is in marked contrast to the extensor response of the toes in the sign of Babinski. It is thus clear, as it has been to other workers who have studied the dog and cat that the nociceptive flexion-reflex in these animals bears no relation to the sign of Babinski, and that toe extension is not a component of this [*sic*] response." This statement does not correspond with Sherrington's account of the flexion-reflex in dog or cat, and its inaccuracy is the more evident when we recall that the crossed extension reflex of the spinal animal which employs the muscles inhibited in the flexion-reflex includes plantar flexion of the toes.

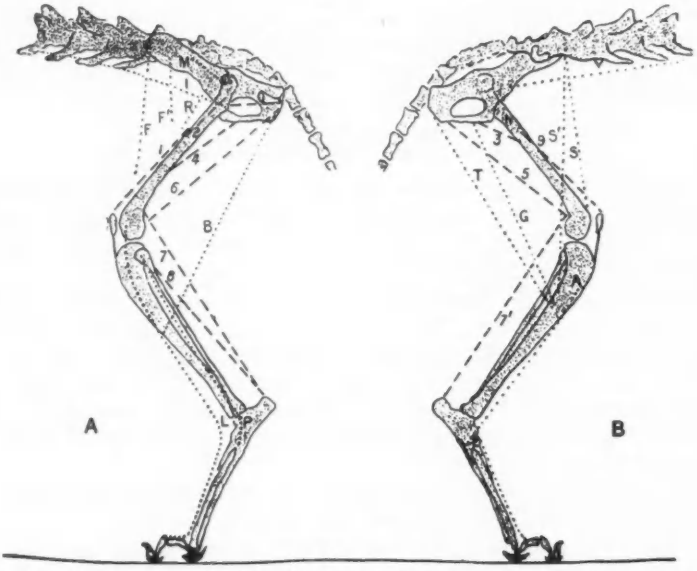

FIG. 2.—Muscles ascertained by direct analysis to be engaged in the flexion-reflex of hind-limb (cat). A, Lateral aspect of limb. B, Medial aspect. Muscles engaged in contraction (dotted lines). Muscles relaxed by reflex inhibition (interrupted lines).

A. Tibialis anticus
B. Biceps femoris
E. Extensor brevis digitorum
F. Tensor fasciæ fem. (long.)
Fl. „ „ „ (brev.)
G. Gracilis
I. Psoas magnus
L. Extensor long. digitorum
M. Gluteus minimus
N. Pectineus
P. Peroneus longus
R. Rectus femoris
S. Sartorius (lat. band)
Sl. Medial band
T. Semitendinosus
Y. Psoas parvus

The following figures from Sherrington's 1910 paper on the flexion and other limb reflexes in spinal and decerebrate dog and cat will perhaps make clear to the reader what and where are the muscles which engage in the flexion-reflex.

The phenomena of "local sign" obtain in the flexion-reflex of the experimental animal as in that of man, and are fully described by Sherrington.

Of the associated crossed extension reflex he says, "The stimulus which evokes the flexion-reflex in the stimulated limb commonly at the same time evokes certain reflex movements elsewhere. In the fellow limb of the crossed side the movement is almost invariably extension . . . In some instances the crossed reflex is unobtainable . . . Reciprocal innervation though exercised in this reflex equally with the flexion-reflex is exercised in exactly the reverse direction." The receptive field of the crossed extension reflex includes that of the homolateral flexion-reflex together with the groin and ischial regions.

Finally, in the decerebrate preparation the flexion-reflex is commonly diphasic. "After withdrawal of the stimulus which excites the reflex flexion there ensues a well-marked extension of the limb. This is more than a mere return to passive extension . . . It is a rebound contraction of those muscles inhibited during the flexion phase."

This state of affairs, so closely paralleled in the flexion-reflex of man, when evoked by adequate stimulation of the sole, is strong confirmation of the homology between the two phenomena. On no other interpretation of the sign of Babinski than that it is a part of a nociceptive flexion-reflex can we account for these crossed phenomena in man. The point is one upon which Hoff and Breckenridge are silent.

The Experimental Observations of Hoff and Breckenridge

In the introduction to this review, the thesis was stated that of themselves animal experiments can neither confirm nor be used to rebut clinical observations made on man, though a comparison of the two may establish or fail to establish an homology between them.

Thus, the submission that the Babinski plantar response is an integral element in a nociceptive flexion-reflex in man can in no sense stand or fall by any animal experiments that Hoff and Breckenridge can bring forward. These can be relevant only to the question of an homology: namely, is this reaction in man homologous with the nociceptive flexion-reflex (Sherrington) in animals?

These two authors approach this question in two ways, by making statements as to what the flexion-reflex as described by Sherrington really is, and by producing some animal experiments of their own.

So inaccurate are their quoted statements about the former that it is difficult to believe that they have given the subject serious study.

Sherrington's analysis and description of the limb reflexes of the decerebrate and spinal animal was published in 1910, and it might be thought that the advance of knowledge since that day, and the application of new techniques, had led to revision of the conclusions formulated by Sherrington so long ago. This appears not to be the case. In their monograph on reflex activity of the spinal cord (1932), Sherrington and his four distinguished collaborators, though they added to the original analysis, took nothing from it, and of the more recent summary to be found in Fulton's textbook of the physiology of the nervous system (1946) the same may be said.

No minute experimental analysis of the limb reflexes, such as Sherrington's in the case of the flexion-reflex, has since been carried out, with its myographic study of almost all the limb muscles individually. But in connexion with the plantar component of this reflex in apes (the homologue of the Babinski response in man), the "clinical" observations of Fulton and Keller (1932) are of considerable significance. They were made after cord transection, or semisection, and after cortical ablations, in acute and chronic preparations in the monkey and in apes.

The experiments of Hoff and Breckenridge, although far more numerous (over 300 dogs and over 50 cats), all dealt with the acute decerebrate preparation, and their observations made thereon are of a far less detailed character than those of their predecessors, and they come to directly opposite conclusions in most respects.

They present no myograms or electromyograms, but only three photographs of the distal half of one apparently protracted forelimb and of the crossed fore-foot, with no indication or information of the posture of the animal or that of its head. A less adequate and informing graphic distillation of the findings in such a holocaust of animals it would be difficult to conceive.

What the authors describe in the decerebrate preparations they studied may, in anticipation, be said to be in essential respects different from the findings of Sherrington, or of Fulton and Keller.

They record reflex reactions obtained from the foot of two distinct orders:

(1) "*A Typical Mammalian Nociceptive Flexor Response*" [*sic*].

The *receptive field* is almost any area on sole or dorsum of foot. The *stimulus* is "a pinch such as would in a normal animal produce a response as though to pain." The *response* is flexion at hip, knee, ankle, toes. (Note that here flexion of ankle and toes must be taken to mean plantar flexion.)

(2) *A non-nociceptive Cutaneous Response which they claim to be the Homologue of the Human Babinski Plantar Response.*

The *receptive field* is the sole of the foot, round the base of the toe pads and between the pads. The *stimulus* is palpation by fingers, light stroking or a light pinch of the dew claw. The *response* is flexion at hip, knee and ankle, with dorsiflexion of the toes.

This last is a curious combination, that of plantar flexion of the ankle and dorsiflexion of the toes, for nothing like it has before been recorded; curious in another sense also, for we have seen that when the ankle is free to move, the extensor longus digitorum dorsiflexes the ankle.

There is scarcely any detail, relevant to the Babinski plantar response (i.e. its homologue in animals), in which this account does not differ from the accounts of Sherrington and of Fulton and Keller.

Thus, the latter find that light stimuli may evoke plantar flexion of the foot in the spinal baboon, while stronger stimuli evoke dorsiflexion, which is the opposite of what Hoff and Breckenridge describe.

Moreover, the authors have set out specifically to establish an homology between a plantar response in the lower limb of man (the Babinski response) and one in the hind-limb of the decerebrate dog and cat. They maintain that both consist of dorsiflexion of foot and toes, that both have the same receptive field, the sole of the foot, and both the same adequate stimulus, light touch.

They purport to illustrate this crucial response in their animals by three photographs, but plantar responses are not what they have illustrated. Having artificially increased the receptive field to include wide regions of the body by administration of a substance, d–l Dromoran: surely unnecessarily if their response is a constant finding in the simple acute decerebrate preparation in over 350 animals, they have chosen the forelimb and have placed their stimuli above the elbow. Why picture something other than what they are submitting as their essential discovery; i.e. a non-nociceptive homologue of the Babinski plantar response, obtained from the pads of the hind feet?

Thus there are features in these experiments as recorded and as illustrated that may convince the reader that results so incompatible with those of previous observers, from Sherrington onwards, need confirmation before they can be unreservedly accepted.

Probably a more intensive and precise study of a much smaller material by such methods as those employed by Kugelberg offers the best prospects of clearing the confusion created by these experiments.

The Babinski Plantar Response and the Pyramidal System

Hoff and Breckenridge do not attempt to substantiate their view that only convention and tradition link the Babinski plantar response with defect of pyramidal system activity. They pass their responsibility in this

regard to Lassek, whose monograph (1954) maintains this view. He contributes no observations of his own, but bases his conclusion upon his reading of the clinical and pathological literature on the subject. He challenges what he calls the "prevailing view" that the sign of Babinski is a sign of pyramidal tract *degeneration*. This view does not prevail, for since Babinski's original discovery of his sign it has been known that the sign may appear transiently in temporary states of disorder of cerebral function, as in hepatic coma, hypoglycæmia, after epileptic fits and in certain intoxications: in a word, from what we now speak of as biochemical lesions.

Lassek further states that "for about a century, it has been continuously taught that degeneration of pyramidal fibres, caused by various types of pathological lesion, produces the classical syndrome of paralysis of the spastic type." Yet the literature abounds in studies in which spastic paralysis is recorded in the absence of secondary degeneration of the pyramidal tract, or indeed of other long descending tracts, while the example of disseminated sclerosis has made this matter a commonplace.

His point of view leads Lassek to suppose further that in the absence of pyramidal degeneration in these circumstances we must look to lesions of other pathways for an explanation of paralysis.

But where shall we look? For the absence of descending degeneration of the pyramidal tract in many cases of spastic paralysis is accompanied by a similar absence in all other descending tracts, and his view leaves us with no possible explanation for paralysis below a focal cord lesion when this degeneration is not present.

Nathan and Smith (1955) also dispute the relation of the sign of Babinski to pyramidal defect, basing their conclusions upon their own very incomplete review of the literature and some original studies of the spinal cord after cordotomy. They conclude (1) that "to regard the Babinski response as a spinal reflex whose manifestation is prevented by the functioning of one, and only one, tract, is an oversimple conception of neurophysiology", and (2) that this response is a pathological one that may be taken to mean no more than that there is an abnormality somewhere within the nervous system.

Their first conclusion, stated in the language of physiology, seems to be that other descending pathways in addition to the pyramidal system probably transmit impulses arising in the brain, which, when the nervous system is intact, inhibit the development of the Babinski response. Their second conclusion goes further and is almost a scientific nihilism comparable with Lassek's equation; no secondary degeneration, no impairment of function, for in effect, their conclusion is seen to exclude all long descending tracts in the cord, singly and severally, from being concerned in the Babinski response, and makes this sign one of indefinable significance with no grounds for its appearance.

In a survey of Babinski's contributions to the subject the authors make a number of trenchant criticisms of him. It has to be said that most of these have no foundation, and are incompatible with a serious reading of his papers. Since their case largely hangs upon these criticisms, it is necessary to deal with them.

(1) *That Babinski described two forms of abnormal plantar response.*—This is not the case. In his brief original paper of 1896, he confined himself to what at that time he had observed, namely, the limb flexion with dorsiflexion of foot and hallux. In his 1898 paper he added the details which I have cited in full (cf. p. 531) concerning the receptive field on the sole and the participation of the other toes in dorsiflexion. In 1903, he added yet another detail, the common but inconstant fanning of the other toes, and in deference to the requirements of accuracy the relevant passages from his very short paper must be given. Speaking of abduction of the toes he says, "L'excitation de la plante du pied provoque parfois, entre autres mouvements réflexes, une abduction plus ou moins marquée d'un ou de plusieurs orteils . . . Mon attention a été attirée aussi, depuis assez longtemps, sur ce phénomène que j'ai observé à l'état normal ainsi qu'a l'état pathologique. Mais chez les sujets sains il est rare, et quand il existe il est peu prononcé, tandis que chez les malades atteints d'une perturbation du système pyramidale il est bien plus commun, sans l'être toutefois autant que l'extension du gros orteil, et il est parfois très marqué". He goes on to say that it is particularly developed in congenital lesions and in normal infants, and concludes that "ce fait qu'il peut exister à l'état normal m'empêche d'attribuer à ce phénomène l'importance fondamentale qui appartient à l'extension du gros orteil, caractéristique d'une perturbation du système pyramidale."

The reader may form his own conclusions as to whether this final comment upon an item in the fullest possible development of Babinski's "phénomène des orteils" justifies the statement that he described not one but two abnormal forms of plantar response.

Elsewhere in their paper Nathan and Smith maintain that in the absence of abduction of the toes, the Babinski response cannot be said to be present. This was not Babinski's view, nor is it that of neurologists as a body, and in any case it is inconsistent with the claim that he described two forms of abnormal plantar response.

(2) *That Babinski neglected to establish his correlation of his sign with disorders or lesions of the pyramidal system.*—This is not the case, for in his paper of 1898 he discusses this matter at some length, and shows himself fully aware of his responsibility in the matter. The relevant passages are far too long for citation here, but the reader may be referred to them.

There was an error into which, with his recent critics, Babinski did fall, however, and this was in believing that an absence of secondary degenera-

tion in the pyramidal tracts in the spinal cord allowed him to assume the perfect functional integrity of the tract.

We must remember in this connexion that all this was sixty years ago when views now no longer tenable were reasonably held.

As the series of cases in respect of which he first formulated his views on this matter is now invoked by Nathan and Smith, the paper in which he described them must be considered. It had the significant title, "Sur une forme de paraplegie spasmodique consécutive à une lesion organique et sans dégenération du système pyramidale."

Three cases are reported: in the first the plantar response remained normal throughout, in the remaining two the Babinski response was present throughout the period of observation. In none of the three was a secondary descending degeneration of the pyramidal tract seen, and thus Nathan and Smith, like Dejerine before them, find in this series a ground for dissociating the Babinski response from pyramidal tract lesions.

But even the most cursory reading of the case records shows that this conclusion does not hold, for Case 1 was one of extracerebellar tumour, and not one of spastic paraplegia.

Case 1. Extracerebellar tumour (depicted in 3 line drawings).—Since operation was not performed, this patient died unrelieved, demented, blind, with persistent headache and sickness, emaciated and with his legs in flexion-contracture. On admission he was not paralysed, his tendon reflexes and plantar responses were normal throughout. Some months after admission to hospital, his general state was such that he became bedridden and thereafter his legs went into flexion contracture. Cerebellar tremor in all limbs developed. The pyramidal tracts showed no descending degeneration.

Under conditions widely prevailing half a century ago, this contracture was a common fate of dements and of patients dying of inoperable malignant disease and long confined to bed. The condition they presented was not that of true spastic paraplegia-in-flexion. Yet at a time when his ideas as to the syndrome so named by him were only in process of formation, it is not remarkable that he should have been in error in such a case.[1]

However, the two remaining cases were true examples of paraplegia-in-flexion, the one being a case of spinal cord compression, the other one of multiple sclerosis. Both showed the Babinski plantar response throughout. Case 2 is the more important of these.

[1]During the years 1912–13–14 when the writer was working upon the observations recorded in his paper of 1914, many visits to infirmaries for the chronic sick revealed numerous patients with legs flexed in contracture, but with neither history nor signs of organic nervous disease. Less common were true cases of paraplegia-in-flexion, as these are described in the paper in question. On the other hand, it is only in such circumstances that the paralysed lower limb in an old residual hemiplegia goes into flexion contracture from its characteristic posture of extension and external rotation.

Spinal cord compression at 7th thoracic segmental level by a meningioma.—Since surgery was not attempted the man died unrelieved within a few days of his admission to hospital, and after a year's history of progressive weakness of the legs. On admission he was totally paralysed below the level of the lesion, the legs were in flexion, and on being passively extended returned at once to their original posture. Knee and ankle jerks were exaggerated, the plantars of Babinski form.

At autopsy, the cord at the level of a meningioma was considerably compressed and crescentic on cross section. Histological examination showed marked sclerosis at the level of the lesion, the great majority of myelin sheaths had vanished, and there was glial thickening and hyaline changes in the vessel walls. Despite their denudation and swelling a great number of axis cylinders were preserved. *There was no secondary degeneration of ascending or of descending tracts.*

Case 3.—An old-standing case of multiple sclerosis, the patient passing finally into a state of paraplegia-in-flexion, and showing Babinski plantar responses and active associated limb flexion. At autopsy, the characteristic plaques of the disease were present. The usual demyelination was found, with integrity of axis cylinders and no descending degeneration of the pyramidal tracts.

Nathan and Smith's long and confused commentary on these three cases, based as it is upon a mistaken diagnosis, is beside the point, for the two true cases of spastic paraplegia both showed the Babinski response and focal demyelination of the pyramidal tract.

Thus Babinski's errors were two. The first, which he shares with these authors, was in not realizing that his Case 1 was not one of spastic paraplegia, and his second, which he shares with them and with Lassek, was to conclude that the absence of secondary degeneration of the pyramidal tract allowed him to assume its functional integrity.

The question of the absence of secondary long tract degeneration when focal spinal cord lesions are present has been long since clearly expounded by Gordon Holmes (1906) in a paper strangely overlooked by writers on this subject. He reports a clinicopathological study of three cases of spinal cord compression leading to fatally ending paraplegia. Microscopic examination of the spinal cord revealed, at the level of compression, integrity of axis cylinders with demyelination. There was no descending or ascending degeneration of long spinal cord tracts. He says, "In sections cut in the length of the fibres at the level of maximum compression and stained by Bielshowsky's method, the remarkable preservation of the axis-cylinders was at once visible. Apparently normal fibrils could be seen running through areas in which there was great tissue change, that is, vascular congestion, vacuolation of the tissue and neuroglial sclerosis. So numerous were these axis-cylinders even in the thinnest sections, that there could be no suggestion of any numerical diminution."

From this fact alone, he continues, "It may be assumed that the presence of myelin sheaths is necessary for the functions of the tract fibres as conducting strands, and that when they are lost there may be a physiological block in the fibres."

It should not be necessary at this date to pile Pelion on Ossa to establish

that the secondary degeneration of spinal cord tracts, pyramidal or other, subject to focal lesions is not an essential condition of physiological block, for demyelination alone may achieve this.

Returning to Nathan and Smith's grounds for rejecting an association between the Babinski plantar response and pyramidal system defect, we find that the survey of the literature which they provide is strangely incomplete, and likely to mislead readers who do not already possess an adequate familiarity with this literature. For example, like Hoff and Breckenridge, they quote the now familiar case described by Dejerine, Levy-Valensi and Long (*loc. cit.*), in which a total transection of the cervical cord, with flaccid paraplegia presented throughout normal, or flexor, plantar responses, but they do not inform their readers that the fixed deformities of the feet in this patient rendered a movement of dorsiflexion of foot or toes physically impossible. As already related, this criticism has long since been made, and later referred to by Babinski (*vide* p. 533 *supra*), and it renders the case useless for the purpose for which they quote it.

(3) *Babinski's views concerning a non-appearance of his sign after total division of the spinal cord* are not accurately represented by the authors. Writing in 1898, when nothing was known of the clinical evolution of the picture of total cord transection, Babinski cites two such cases reported by Cestan, who examined them, one three hours after the trauma and the other nine hours after trauma. There was no plantar response of any kind in either on these two occasions. Commenting upon these observations, Babinski says that "one has no right to conclude from them that the Babinski response must invariably be absent after transection of the cord."

Time has proved his surmise correct, and we now know that after a brief initial period of plantar areflexia, and with or without a short intervening period of reflex plantar flexion, the Babinski response is characteristically and permanently present in such cases. In this connexion, Nathan and Smith make no reference to the large and carefully analysed series of cases of cord transection reported by Head and by Riddoch (1917), nor the recent series of Kuhn (1950), which place this matter in proper perspective.

Upon the known appearance of the Babinski plantar response after focal ablations of the "leg area" of the human precentral cortex, these authors also remain silent,[1] though there are a few crucial cases in the literature (Walshe, 1935; Bucy, 1944), nor do they refer to the comparable cortical ablations in apes by Fulton and Keller (*loc. cit.*), in which the

[1]The omission is the more remarkable in that in their summary (*Brain*, 1955, 78, 248) of the anatomy of the long descending tracts in man, these authors have recorded that "most of the cells of origin of the cortico-spinal tract are situated in the precentral gyrus, mainly in its upper two-thirds, and in the paracentral lobule."

homologue of the Babinski response infallibly appeared and persisted. Foerster, summarizing his own experience (cited by Bucy) says that appropriately placed precentral ablations in man are followed by the appearance of the Babinski response within from five to ten hours.

Suitable cases must be few, because it is necessary that the lower limb before operation should have had a normal plantar response. Yet this was the case in two of Bucy's series, in which after ablation a previously normal plantar response was replaced by the Babinski response.

Perhaps the "cleanest" case of the kind is that reported by the present writer (1935), for before operation repeated physical examination of the patient in her interconvulsive periods revealed no abnormal physical signs of any kind.

> The patient was a girl of 11 years who for five years had been subject to focal Jacksonian convulsions of the left leg. At operation the upper end of the right precentral convolution was exposed, and the area from which foot movements could be obtained by faradic stimulation was demarcated and excised. The excised tissue was examined by Dr. Greenfield who found it to be characteristic of the area gigantopyramidalis and to be free from pathological change.
>
> The immediate operative result was a slight paresis of the left lower face and the left upper limb, total loss of movements of ankle and toes and a Babinski plantar response (this response having previously been consistently normal). The neighbourhood signs cleared up and six weeks later all that remained was slight hypertonus of calf muscles, increased knee and ankle jerks, weakness of dorsiflexion, eversion and inversion at the ankle and of all toe movements. The Babinski plantar response persisted.

Turning now to the experimental animal, as revealed by the cortical excisions of Fulton and Keller (1932) in apes, on which Nathan and Smith are again silent, we find that focal ablations of the "leg area" in apes are constantly followed by a plantar response in which dorsiflexion of the hallux is present: the homologue of the Babinski plantar response in man.

Here, in these cortical excisions the conditions are far more favourable for establishing or for excluding a relation between the Babinski plantar response and a defect of function in the pyramidal system, than spinal cord sections can possibly be, for in the cortex the pyramidal system is less "contaminated" by admixture with or contact with other long projection systems than at any spinal anatomical level.

In short, it is a grave defect in what purports to be a balanced survey of the relevant literature upon the relationship of the Babinski plantar response to the pyramidal system, that it does not present the evidence in support of the existence of such a relationship. To dismiss all the known facts of cortical excision in this connexion by the statement that "it is sometimes stated that the removal of the function exercised by area 4 of Brodmann causes the Babinski response to appear" is a meiosis that actively misleads.

The authors' own contribution is limited to the microscopic study of

a series of cases in which cordotomy had been performed in patients in whom, prior to operation, the plantar responses were normal.

These cords have been examined at the level of section to see what descending tracts must be assumed to have been severed. We are given no details of the range of staining methods employed to reveal what was abnormal in the sections.

The diagrams showing the lesions indicate how unpredictable must be the depth and extent of cordotomy, for the sections seem scattered almost at random over the lateral and ventral columns, are sometimes predominantly ventral, sometimes predominantly lateral, and of varying depth.

Perhaps the most remarkable of the diagrams is a series of five showing the sections following which the plantar responses remained normal. If these five are superimposed, it is found that only a narrow zone lateral to one posterior horn is intact in all five, and if this is to be regarded as the situation of the descending pathway, the activity of which inhibits the appearance of the Babinski response, it would appear that this lies in the zone of short propriospinal fibres and must act bilaterally.

Taking these diagrams as a whole, and reading them as do the authors, they may be taken to show—*only if we accept the histological criterion as a valid one for functional integrity*—that there is no tract whatever descending from the brain, the state of activity of which we can place in relation to the Babinski plantar response. We are in the same kind of position as that in which Lassek has left us; namely, that there is no discernible explanation in terms of neurones for the appearance of an abnormal reflex reaction which we have all observed thousands of times. Nathan and Smith have proved too much, and have provided the *reductio ad absurdum* of the histologist's endeavour to be the highest court of appeal in the matter of functional integrity.

To accept their conclusion that the Babinski response is no more than an indicator of disorder of function or of structure at some situation within the nervous system, not even to be guessed at on the strength of this sign, would make nonsense of the discipline of clinical neurology and would shackle us diagnostically if we adopted it as a working hypothesis. For we perfectly well know that whatever the microscope may reveal or fail to reveal in dead tissues, the appearance of the Babinski plantar response has a definite localizing value *vis-à-vis* the pyramidal system: a working hypothesis that has been amply justified by the experience of over half a century: and not seldom verified pathologically.

It may well be that the pyramidal system has not yielded up all the secrets of its constitution, origin and activities, and that at some future time research may reveal within what we now call the pyramidal system separable elements, to the state of activity of one of which it may be possible to relate the Babinski response. At present, however, "busy common sense" which has been too long absent from this particular scene, requires

us to look upon the Babinski response as standing in relation to the pyramidal system. Morbid histology cannot be accepted as the final criterion by which we assess functional activity. In 1870 Hughlings Jackson reminded his contemporaries that "functional change must not be confounded with pathological change: though the two must necessarily co-exist." He did not say that functional change must co-exist with *microscopically visible* pathological change. We have only to call to mind those, fortunately uncommon, fatal cases of acute polyneuritis in which during life the symptoms are clearly referable to abrogation of function in peripheral motor nerve fibres, but which at autopsy reveal either no nervous lesion whatever, or at most a slight œdema. Are we not entitled to make localizing diagnoses in such cases, basing ourselves on previous clinicopathological experience, even though we know that in this particular order of illness we may never be able to verify them?

The modern concept of the biochemical lesion, and a proper appreciation of the limitations of the histological method, relieve us from a situation so ridiculous.

Conclusions

(1) Babinski's original description (1896) of the sign which bears his name is explicitly that of a reflex reaction consisting of flexion at hip and knee and of dorsiflexion of ankle and hallux, and sometimes of the remaining digits. It is, he tells us, evoked by "piqûre"; a nociceptive stimulus.

Of this complete reaction, it was the dorsiflexion of the toes that became *clinically* significant when its relation to disorders of the pyramidal system became established. Thus the term "phénomène des orteils" was coined by Babinski.

Not until sixteen years later, in 1912, when the occurrence of reflex-flexion of the lower limbs had attracted the attention of neurologists, and the suggestion had been made by Marie and Foix (1912) that the "phénomène des orteils" was no more than a fragment of what had become known as "réflexes d'automatisme médullaire," or "reflexes de défense," did Babinski by definition first separate his toe sign from the distal components of the reaction which he had originally described as a unity, and maintain their qualitative distinctness. It may be said that he never gave any clear, constructive reasons for this view, and it has not been generally accepted.

(2) The present writer in 1914 attempted an analysis of the flexion-reflex in man and came to the conclusion that the Babinski plantar response was an integral part of this, and was sometimes associated with an accessory crossed extension reflex of which the striking component was the crossed plantar (plantar flexor) response.

(3) A comparative analysis of this reflex in man and the nociceptive flexion-reflex described by Sherrington (1910) was also made, and the conclusion expressed that the two phenomena were strictly homologous.

The validity of this view has recently received additional confirmation from Kugelberg's electromyographic analysis of the A and C fibres in this response in man. This has shown that the adequate stimulus for the reaction involves the activity of the A and C fibres: that is, the so-called "fast" and "slow" pain fibres. Further, that the response has two components, a fast and a more powerful slow response, corresponding to the activity of these two afferent paths, and, finally, that stimulation of the large tactile fibres alone is not an adequate stimulus to the Babinski plantar response.

These observations also point the road along which any further attempt to establish the correlation of the Babinski response with the rest of the flexion-reflex must go.

(4) The experiments of Hoff and Breckenridge have been summarized and the conclusion reached that they are obscure and unsatisfactory, and at variance with earlier findings on the flexion-reflex in the experimental animal. The several significant silences in their references to the literature, and their grave inaccuracies in what they do tell us, in so far as these may mislead the reader, are discussed.

(5) In respect of the problem of the relationship of the Babinski plantar response and the flexion-reflex to disorders of activity, with or without structural damage, of the pyramidal system, the views of Lassek and of Nathan and Smith are discussed.

Lassek's opinion, accepted by Hoff and Breckenridge, that there is no valid evidence to correlate the two is shown to be based upon an imperfect understanding of the literature, and an ignorance of the neuropathology of long conducting tracts in the central nervous system when subject to compression or other disease processes. Secondary degeneration, ascending or descending may never ensue, even when functional activity is impaired or abolished, unless the disease process in question actually destroys the continuity of axis cylinders. Lesions involving only demyelination of such tracts may suffice to interrupt conduction in them.

Lassek's postulate that secondary degeneration of a spinal cord tract must be present before we may presume loss of function would leave us with no possible explanation in terms of neurones for very many examples of spastic paraplegia.

Nathan and Smith, as far as can be ascertained, seem to hold similar views about the importance of secondary degeneration. In their review of the literature concerning a relationship between pyramidal system defect and the Babinski plantar response, they do not always accurately represent Babinski's position and they are silent respecting the evidence available in support of the existence of such a relationship.

Their own histological studies of spinal cord lesions produced by the operation of cordotomy—if taken to have the meaning the authors give them—leave us with no long tracts descending in the cord to the states of

activity of which we can relate the state of the plantar response: as between the normal and the Babinski response. This means that it is not possible to account for the appearance of the latter response upon any basis of neuronal activity. This is the scientific nihilism we have already encountered in Lassek's views, ineffectively disguised as its opposite, scientific logic and precision. Further, the conclusion of these authors that the Babinski response, no longer earthbound by any neuronal relations, has no localizing value whatever in respect of structural or functional defects within the nervous system, is the fantastic climax of thinking remote from reality.

Of course, the answer to this is that histological studies have narrow limitations as indices of functional integrity, and these authors have asked of the method what it has not been able to give.

The reviews of the literature which have been referred to here, provide another illustration of the truth that the relevance of evidence is dictated by theory. Up to a point, this is inevitable in observational science, but carried beyond rational limits, it becomes a menace to scientific thought, especially when it can lead to a state of affairs in which crucial evidence upon the relation of the Babinski response to pyramidal system lesions, such as that provided by excisions of the precentral "leg area" in man, is virtually ignored.

(6) Finally, it is submitted that the description and interpretation of the Babinski plantar response given by the writer in 1914 have not been invalidated by subsequent clinical observations, and that these clinical observations, as such, are not in any way dependent upon "confirmation" by animal experiments, which can afford only the means of establishing an homology between a state of affairs in man and a comparable one in the lower animals. At most a sort of mutual reinforcement comes from the establishment of an homology of this kind, but clinical observation stands upon its own foundations.

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COUGH HEADACHE

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THE act of coughing may aggravate headache whatever its cause, but does not so often provoke it. Nevertheless, there are cases in which a physical basis can be found, in which immediate and transient pain in the head is precipitated by coughing. When this is so, other actions such as sneezing, straining at stool, laughing or stooping often have the same effect. This liability is not infrequently observed in cases of intracranial tumour, but is then ordinarily associated with the occurrence at other times of headache which is spontaneous and of a different kind. There is, however, a group of patients having the liability to brief, severe pain in the head precipitated by the factors mentioned, and especially by coughing, in whom no evidence of intracranial or cranial disease is to be found. It is this last group with which this paper is chiefly concerned, but for purposes of comparison I shall first present a few cases in which a similar liability was for some time the only symptom, or at least the predominant symptom, of a condition for which an organic basis was finally discovered or which occurred as a sequel of intracranial operation.

COUGH HEADACHE ASSOCIATED WITH ORGANIC DISEASE

Case 1.—*The liability to transient severe pain in the head on coughing, sneezing, laughing, stooping or straining at stool was for fifteen months the only symptom of a posterior fossa meningioma arising from the under surface of the tentorium. At the relevant time the cerebrospinal fluid pressure was normal, and there was no dilatation of the ventricular system.*

I am indebted to Dr. Michael Kremer for the notes of this patient, whom I saw when she was in hospital under his care. A married woman, aged 50, first attended the Middlesex Hospital as an out-patient on February 5, 1951, with the complaint of severe headache on stooping, coughing, laughing, sneezing or straining at stool. The pain was most severe in the front of the head but also felt in the occipital region, and was bilateral. It followed the precipitating cause immediately, and lasted from a few seconds to two minutes. It was described as a terrible bursting feeling, and its severity was such that she would hold her head in her hands. This liability had been constantly present for one year. She denied headache at any other time and had no other complaints. No abnormal physical signs were discovered except moderate arterial hypertension. Three months later she developed a new symptom. On rising one morning she had severe frontal headache accom-

panied by vomiting and lasting several hours. This subsequently recurred on one or two occasions. She was then admitted to hospital and investigated as a possible case of intracranial tumour. No abnormal physical signs were found apart from the arterial hypertension. Lumbar puncture was performed on two occasions with an interval of twelve days. The cerebrospinal fluid pressure on the first occasion was 80 mm. and on the second 110 mm. The constituents of the fluid were normal. EEGs were recorded by Dr. Parsons-Smith on three occasions, and in all the records there were generalized bursts of 4–6 c/s waves predominant in the frontal areas, more on the left than the right. Dr. Parsons-Smith thought the abnormality consistent with an intra-ventricular tumour. A ventriculogram was performed by Miss Diana Beck, which showed the lateral and third ventricles to be of normal size, shape and position. The fourth ventricle was poorly filled. It was thought possible that it was displaced slightly to the right. Following her discharge from hospital the liability to paroxysmal headache precipitated by coughing and the other factors mentioned continued, but there was no recurrence of the other type of headache for four months. She then had a period during which early morning headache with vomiting occurred almost daily for several days.

On January 8, 1952, she was admitted under Dr. Kremer to the National Hospital, Queen Square. Again no abnormal physical signs were discovered apart from blood pressure readings of 200 systolic and 100 diastolic. An air encephalogram was attempted, but although air reached the cerebral cortex it failed to enter the ventricles. Following her discharge the liability to paroxysmal headache continued. She was readmitted on August 29, 1952, on account of recurrence of early morning headache and vomiting. A further air encephalogram was attempted, again without any air entering the ventricular system. Her third admission was on February 5, 1953, on account of a much more protracted and severe episode of headache and vomiting associated with neck stiffness. Ventriculography was performed and showed the lateral ventricles to be normal in size, shape and position. The aqueduct was kinked forwards and displaced to the right, and the fourth ventricle also displaced to the right. Mr. Wylie McKissock operated on the same day and found a meningioma arising from the under surface of the tentorium and extending backwards to the region of the torcular. It was about 6 cm. in diameter. It was deemed inadvisable to remove the base of the tumour in view of the risk to the large venous sinuses. She was subsequently given deep X-ray treatment. Following the operation the liability to headache on coughing and other actions disappeared, though she suffered a good deal from vertigo and had occasional early morning headache, sometimes with vomiting.

Case 2.—A liability to transient severe pain in the head on coughing, sneezing or straining at stool was for two years the predominant symptom of a cyst of the mid-brain lying within the incisura tentorii. In this case, however, attacks of similar pain had sometimes occurred, without the characteristic provocation.

A married woman, aged 51, was admitted to the National Hospital, Queen Square, under my care on November 11, 1934, with the complaint of an increasing liability for two years to severe, transient headache on coughing, sneezing or straining at stool. The pain was described as beginning either at the root of the nose or in the temples, quickly spreading up the sides of the head, gripping the head as in a vice and radiating into the nape of the neck. On three or four occasions it had radiated down the neck into the shoulder blades. It immediately followed the precipitating cause and lasted from five to ten minutes and was very severe, leaving a soreness afterwards. She could remember a few such attacks occurring without any provocation.

On examination she showed slight weakness of the right face and hand and occasional choreiform movements in the right hand. At lumbar puncture the cerebrospinal fluid pressure was 210 mm.

She was readmitted on March 3, 1935, having recently developed spontaneous attacks of headache of much longer duration and different quality associated with vomiting. She had also had diplopia and vertigo. The choreiform movements in the right hand were more continuous. Ventriculography revealed a symmetrical internal hydrocephalus. Mr. Julian Taylor performed a suboccipital exploration which showed a cerebellar pressure cone, and she died soon after the operation. Post-mortem examination revealed a cyst arising within the mid-brain, confined to the left half of its tegmental portion. It had bulged into the upper end of the fourth ventricle and obliterated the iter. Histologically the cyst was lined with a thin epithelial membrane resembling flattened ependymal cells. There was no evidence of tumour in the surrounding tissues.

Case 3.—A liability to transient, severe pain in the head on coughing, lifting, laughing or straining at stool was for two years the predominant symptom of Paget's disease of the skull with basilar impression. The cerebrospinal fluid pressure was normal, and there was no ventricular dilatation. Following an air encephalogram the patient was completely relieved of the liability to headache and remained so one month later.

A married woman, aged 59, was admitted to Guy's Hospital on February 11, 1955, under my care with the major complaint of pain in the head provoked by coughing, lifting or straining at stool. This liability had been present for two years and at the same time she became aware of a puffing noise in the left ear, intermittent and especially at night, which had continued to the present time. The pain in the head was described as bursting and of bitemporal distribution. It was very severe but lasted only about three minutes. She never had it without one of the provoking causes mentioned. On examination there were no abnormal physical signs but a systolic bruit was audible behind the left ear. X-rays of the skull showed Paget's disease involving the vault and base, including the orbital roofs, sphenoidal bones, dorsum sellæ and posterior clinoids, with a moderate degree of basilar impression. Lumbar puncture gave a cerebrospinal fluid pressure of 145 mm. with normal constituents in the fluid. An air encephalogram showed a normal ventricular system. There was no more than the ordinary reaction to this procedure. One month later she reported as an out-patient stating that since the air encephalogram she had been able to cough, laugh and strain without headache for the first time for two years, for which she was very grateful.

Case 4.—A liability to transient severe pain in the head on stooping, coughing, sneezing or straining at stool for three years was the only symptom of Paget's disease of the skull with basilar impression.

A married woman, aged 63, was admitted to the National Hospital, Queen Square, on February 23, 1955, under my care with the complaint of pain in the head on stooping, coughing or straining at stool. The liability had been present for three years. The pain was mainly at the back of the head, but also involved the frontal and vertical regions. It was described as sharp and severe, but its duration was only about three minutes. Recently with the pain she had experienced giddiness, which she described as a sense of being unbalanced. She had been subject to attacks of migrainous headache since the age of 16, which she described as quite different from the present complaint. Apart from severe deafness due to otosclerosis she presented no abnormal physical signs. X-rays revealed Paget's

disease involving the whole of the skull with a moderate degree of basilar impression. The cerebrospinal fluid pressure was not measured. The fluid contained no abnormal constituents. An air encephalogram revealed a normal ventricular system. There was no improvement in her headaches after this procedure.

Case 5.—A liability to transient severe pain in the head on coughing, straining at stool, stooping and blowing the nose was the first symptom of Paget's disease of the skull. After continuing for several months this liability disappeared for four years, when it recurred and had continued until the patient was observed, and the diagnosis was first made ten years after the original onset. There was an extreme degree of basilar impression.

A married woman, aged 50, was admitted to Guy's Hospital in 1951 under Dr. M. J. McArdle, who kindly allowed me to see her. Ten years previously during an attack of influenza she began to experience sudden severe pain in the head on coughing, straining at stool, stooping, or vigorous nose blowing. The distribution of the pain was frontal, vertical and occipital and would last for some minutes. The liability continued for several months and then disappeared completely for four years. It then recurred and had continued until the present time. Independently of this kind of headache she had for several years had spontaneous attacks of headache lasting for some hours and accompanied by vomiting. On examination the fundi and visual fields were normal. There was a moderate degree of perceptive deafness on both sides. The right corneal reflex was diminished. There was bilateral palatal weakness. Both lower limbs were a little spastic and weak. All the tendon jerks were increased, and both plantar responses were extensor. There was no sensory impairment. The X-rays showed generalised Paget's disease of the skull with a severe degree of basilar impression.

Case 6.—A liability to transient severe pain in the head on coughing, sneezing, laughing, stooping or straining at stool developed several weeks after the removal of an acoustic neuroma and had persisted for a year when the patient was last seen. There had been considerable recent improvement following a respiratory tract infection during which coughing was especially painful.

For the opportunity of seeing this patient on February 2, 1956, I am indebted to Mr. D. W. C. Northfield, who had removed a right acoustic neuroma on January 19, 1954.

A married woman, aged 61, when I saw her, had for several years before her operation noticed progressive right deafness, followed more recently by numbness of the right face and finally by watering of the right eye, doubtless due to facial weakness. At no time had she suffered from headache before the operation. Following this while in hospital she had intermittent early morning headaches of generalized distribution associated with retching. These gradually became less frequent and had ceased within four months of the operation. She was kept in hospital for seven weeks owing to an infection of the respiratory tract. During this period she was much troubled by coughing, which, however, caused no headache. Some time after returning home she found that if she coughed, sneezed, laughed, stooped or strained at stool she had an immediate blinding pain right through the middle of the head, which as it died away disappeared last in the occipital region. The pain lasted about half a minute with no aftermath of ache. This liability continued unabated so that she came to dread any of the provoking causes. In December 1955 she had an upper respiratory tract infection, the first since leaving hospital, and coughing was an agony. When, however, she got rid of her cough she noticed that the liability was considerably less. Owing to

domestic difficulties she was obliged to engage in heavy work about the house and found that she could now stoop and lift without pain in her head to a degree that was previously impossible. She could sometimes cough and even strain a little at stool without pain.

In all these cases the character and duration of the headache and its provoking causes were substantially the same. In only one instance, Case 2, had this kind of headache ever occurred without such precipitating cause. In 3 cases the cerebrospinal fluid pressure was measured and found to be normal. In Case 2 it was 210 mm., but the symptoms under discussion had then been present for two years. In 3 cases pneumoencephalography at the relevant time showed no ventricular dilatation. In Case 6 the symptoms developed several weeks after the removal of an acoustic neuroma, and there was no clinical evidence at that time suggestive of increased intracranial pressure. It seems, therefore, highly improbable that this particular variety of headache could be interpreted in terms of increased intracranial pressure *per se*. All 6 patients had, or had had, disease capable of causing pressure changes within the posterior fossa. In Case 1 there was a tumour growing from the under surface of the tentorium and displacing the iter and the fourth ventricle; in Case 2 an expanding lesion lay within the incisura tentorii; in Case 6 after removal of an acoustic neuroma there were symptoms suggesting a loculated collection of fluid beneath the tentorium before the cough headache developed; and in the three cases of Paget's disease with basilar impression crowding of the structures within the posterior fossa may be presumed. It appears then that in some way the increased venous pressure resulting from coughing, or actions producing the same effect, was capable in the presence of abnormal pressure within the posterior fossa of causing the headache. In the normal person, coughing, however violent, does not cause headache, and perhaps the first question to be answered is why it does not. That it causes an increase in intracranial pressure from venous dilatation we know from observing the response when measuring the cerebrospinal fluid pressure. The intracranial venous dilatation is presumably obtained at the expense of the cerebral capillaries and expulsion from the cranial cavity of such a proportion of the cerebrospinal fluid as can be accommodated by the spinal subarachnoid space. Under these conditions it has been argued by Pickering (1948) that there should be a displacement of the brain towards the foramen magnum. This would involve traction upon the structures, vascular and dural, anchoring the brain to the skull which are known to be sensitive to this form of stimulation. Yet no headache results, presumably because the degree and direction of traction are inadequate to cause it.

Lumbar puncture headache is aggravated by jugular compression, and from my own observations may be provoked by coughing when temporarily absent. Here it may be supposed that the additional factor

is depletion of cerebrospinal fluid with consequent intracranial venous dilatation, which is further increased by jugular compression or coughing. The potential capacity of the spinal theca also is increased. Therefore although the direction of cerebral displacement is normal its degree is excessive. The observations of Marshall (1950), however, have cast doubt upon this interpretation. He found patients with characteristic lumbar puncture headache who at the relevant time had normal cerebrospinal fluid pressures, and others whose pressures when recorded after the same interval were as low as zero who had no headache at all. This raises the possibility that the lumbar puncture headache is not entirely due to hydrodynamic factors, but may depend on injury to intracranial pain-sensitive structures as the result of excessive stretching when the fluid was withdrawn.

The immediate aggravation by coughing of pre-existing headache in patients with intracranial space-occupying lesions is well known. In such cases there is already displacement of the brain and traction upon pain-sensitive structures, which is presumably further increased by venous distension with consequent cerebral shift. Some mechanism of this kind may be presumed to have been the cause of the cough headache in the patients described. The precise nature of the pain-sensitive structure involved is a matter for further discussion. Experienced observers (Penfield, 1934; Northfield, 1938; Wolff, 1948) of the effects of stimulation during intracranial operations under local anæsthesia are agreed that pain may result from traction upon the walls of the dural venous sinuses and their tributaries. Penfield (1934) and Wolff (1948) both record pain from stimulation of the transverse sinus and torcular referred as far forward as the forehead and eye. All three observers have noted headache of widespread distribution from pressure upon the tentorium. Penfield (1934) considered the large dural sinuses to be the important intracranial pain areas and believed that traction upon their walls was the probable source of pain from pressure upon the falx or tentorium. He also observed that wherever there were adhesions between the arachnoid and dura these were particularly sensitive to pain. In a further paper (Penfield and Norcross, 1936) he described localized adhesions of this type in patients with headache following head injury, some of whom were cured either by operative dissection of the lesion or by lumbar insufflation of air. In one of the cases submitted to operation under local anæsthesia when the adhesions were separated the patient complained of pain, which he "likened to the pain he had habitually on coughing or sneezing." The possibility of adhesion between a mobile structure and a non-mobile pain-sensitive structure must be taken into account in certain of the 6 cases described above. It would serve as a convenient explanation of the immediate disappearance of the liability to cough headache following an air encephalogram in Case 3 and the

considerable improvement in Case 6 following a period of excessive and extremely painful coughing due to a respiratory tract infection. It might also account for the spontaneous remission of four years in Case 5.

Cough Headache without Evidence of Organic Disease

The 21 patients reviewed under this heading form a homogenous group in so far as in every case the presenting complaint was of transient severe pain in the head provoked by coughing and similar effort, and in none was there any evidence from clinical enquiry of any demonstrable physical basis. In few instances, however, were subsequent investigations carried to the point of excluding a space-occupying lesion. The reasons for this omission were that in most cases the symptom, though troublesome, was not disabling. Some of the patients were already improving when they were first seen. In others the symptom was of such long standing that it seemed, in the absence of physical signs, very unlikely that a tumour was present. A number of them were elderly and frail and likely to tolerate pneumo-encephalography badly. In most cases the advice given to the family practitioner included a warning that an intracranial tumour might be present and the recommendation that if after a time there was no spontaneous improvement the patient should be admitted to hospital for full investigation. In only 4 cases, however, was this carried out. In some instances this may have meant that the patient improved, or that he sought advice elsewhere. Unfortunately only 17 cases were adequately followed up owing to the difficulties ordinarily encountered together with the disruption of the war. All the patients in this group were seen in private consulting practice between the years 1929–1939, and 1945–1955. With these reservations in mind I believe there is sufficient evidence to show that cough headache may occur as a benign syndrome.

Cases Ending in Recovery

In 9 cases there was eventual recovery, and this being the best evidence of benign character they will be first considered. They may be divided into two sub-groups, the first comprising those patients who admitted no headache except with provocation, the second including the remainder. There were 4 patients in the first group and 5 in the second. Brief details of these cases follow.

Pain only on Provocation

Case 7.—A married woman, aged 38, with no relevant previous illness seven weeks after an operation for colporraphy began to have headache on coughing, stooping, sneezing, straining at stool or hearty laughter. The pain was severe and was described as bursting and of generalized distribution. Its duration was about two minutes. She volunteered that she could cough without pain when lying down. She admitted no spontaneous headaches and had no other complaints. The

liability continued and at the end of six months she was investigated by Dr. A. M. G. Campbell. The X-rays of the skull showed no abnormality. An EEG showed non-specific dysrhythmia. The cerebrospinal fluid showed a pressure of 120 mm. and contained no abnormal constituents. The Wassermann reaction was negative and the Lange curve normal. Following lumbar puncture she had severe headache aggravated by the vertical posture, but on getting up after a few days found that she had lost the liability to headache on coughing and straining and for a few weeks felt a new person. The liability then returned and was present when I saw her on June 11, 1951. There were no abnormal physical signs. Bilateral jugular compression did not evoke headache. At my suggestion Dr. Campbell subsequently performed an air encephalogram, which showed no abnormality, and reported later that following this procedure she again recovered. There was a subsequent brief relapse with final complete recovery, and she reported herself five years later in excellent health.

Case 8.—A man aged 60 presented in June 1949, with the main complaint of headache on coughing, sneezing or stooping for the past fourteen months. The pain was described as sharp in character and vertical and bi-frontal in distribution. It lasted a few minutes, followed by an ache for a further few minutes. For the past five weeks he had noticed a left high-pitched, continuous tinnitus. He had recently become anxious and depressed. Fifteen years previously he had had a depressive illness. There were no abnormal physical signs. X-rays of the skull were normal. Examination by an aural surgeon revealed left Eustachian obstruction without other abnormality. He subsequently developed a depressive illness requiring treatment with ECT. On recovery from this illness he had lost the liability to headache, which has not returned in the subsequent six years.

Case 9.—A married woman, aged 42, presented on November 23, 1936, with the complaint of headache on stooping, coughing or laughing which had been present for six months. The pain was very severe while it lasted, the duration being five to ten minutes. It was referred to the top of the head and above the eyes. She admitted no headache without provocation and had no other complaints. In the past twelve years she had had several epileptic seizures of a generalized character. There were no abnormal physical signs. X-rays of the skull were normal and examination by an aural surgeon showed no abnormality. The liability to headache continued for a further two years and then gradually disappeared and had not returned when she was last heard of nine years after I first saw her.

Case 10.—A married woman, aged 73, was seen on August 16, 1932, with the complaint that for the past three months she had experienced severe pain in the head on coughing, sneezing, stooping or lifting heavy objects. It might also be provoked by lying down quickly. The pain was referred to the top of the head, sometimes, and especially on stooping, radiating to the front. It was very severe for a few minutes, and was followed by a dull ache, which might persist for an hour or two. During the same period she had sometimes found herself unsteady on her legs so that she feared people might think she was drunk. She had no other complaints and admitted no spontaneous headache. Six months before the onset of her present complaint she had had a minor head injury without concussion. There were no abnormal physical signs. X-rays of the skull were normal and the report of an aural surgeon was negative. Seen again three months later she had not improved. She wrote, however, a year later to report that she had begun to improve three months earlier and was now completely recovered.

Headache Sometimes Present without Provocation

All 5 patients in this sub-group presented with the complaint of pain in the head on coughing and other effort, but either before or after the onset of this symptom experienced spontaneous and usually more prolonged headache. The cough headache differed in no important particular from that related in the previous cases and will not therefore be described in full detail. None of these patients showed any abnormal physical signs. X-rays of the skull were normal in every case.

Case 11.—A man, aged 60, was seen on September 8, 1947. Two months previously he had developed the liability to transient severe pain in the top of the head on coughing or stooping. Seen again four months later he still had this liability but also complained of intermittent, generalized dull headache without provocation. Six months later his doctor reported him greatly improved, and eighteen months after this completely recovered following the extraction of a tooth with an apical abscess.

Case 12.—A man, aged 37, who had had no previous illness except malaria was seen on August 24, 1936, with the history that eighteen months previously he had begun to have occasional headache, at first only once in two or three weeks. It would be felt either at the back of the head or in the forehead and last a few minutes only. As time went on these headaches, of spontaneous occurrence, became more frequent, more severe and more protracted. Six months before I saw him he began to have severe bursting pain at the top and sides of his head on coughing, straining at stool or hearty laughter. The liability was constant. He continued to have occasional spontaneous headaches. The investigations included a lumbar puncture, after which all headache disappeared and had not returned six months later. The cerebrospinal fluid pressure was 170.

Case 13.—A medical man, aged 67, was seen on May 3, 1933. Eight months previously he had begun to have headache, bi-frontal, dull and intermittent, relieved by aspirin and not aggravated by coughing or stooping. Three months later this was replaced by a liability to transient severe pain in the anterior half of his head on coughing, sneezing or stooping, which he had had continuously for five months. Five weeks after this he had an infected molar tooth extracted and reported later that within a few days the liability had entirely ceased.

Case 14.—A man, aged 73, was first seen on November 4, 1929. Three months previously he had begun to have a persistent bilateral occipital ache sometimes accompanied by intermittent sharp pain in the right malar region. In the course of the next two months this disappeared and was replaced by a liability to brief severe pain of a bi-fronto-parietal distribution on coughing, sneezing or stooping. He was observed at intervals of a few months and for a year reported little improvement, but by March 20, 1931, was completely recovered and had resumed his daily toe-touching exercises without any head discomfort.

Case 15.—A man, aged 65, was seen in December 1945, with the complaint that for eighteen months he had had pain in the head on coughing, stooping or sneezing. This was immediate and severe for a few minutes, being followed by a dull ache which might last for an hour. It was at first vertical in its situation, later tending to spread fanwise into both frontal regions. He also had occasional spontaneous headache in the same distribution of a shooting or throbbing character. Apart

from blood pressure readings of 205 systolic and 105 diastolic he showed no abnormal signs. He was advised to use a nasal douche for the treatment of catarrh which was the cause of excessive coughing. He was reported to have lost the liability to headache a few months after I saw him. Ten years later he was alive and well and had no recurrence.

Discussion

In 6 other cases of the series improvement was recorded. The duration of the symptoms in these cases was as follows: eighteen months; two and a half years; three years; three and a half years; five years; and twelve years. No symptoms suggestive of intracranial tumour had developed in this time. In each instance the patient reported that coughing or other effort no longer invariably caused pain, though the liability was still present in some degree. 2 patients were reported to have died; one at the age of 79 from cardiac failure, having suffered from cough headache for two and a half years; the other at the age of 78 from a coronary thrombosis with a two-year history of cough headache. Neither had developed any symptoms of tumour or other cerebral disease. 4 patients were untraced.

Of the whole series 14 patients never experienced headache apart from coughing or other provocation. In the remaining 7 at some time during the illness there had been headache of spontaneous occurrence, which in every instance save one had preceded the onset of cough headache.

If it be conceded from the evidence that has been presented that a benign syndrome of cough headache exists, the next question is that of its cause, taking into account both the situation of the lesion and its pathology. With regard to the former, comparison with the syndrome as observed in cases with a proved organic basis suggests that a common mechanism be sought, and that the source of the pain lies within the posterior fossa. Some support for this localization exists from the observation that of 9 patients in the benign group who had other complaints associated with that of cough headache 5 had symptoms of disturbed auditory or vestibular function. Of these 3 had vertigo, which was in one case established by Dr. Hallpike as positional; one had bilateral tinnitus and deafness; and another unilateral tinnitus. Another patient complained of a feeling of fullness deep to the drum of the right ear.

With regard to the mechanism of the pain, 2 patients volunteered that quick rotation of the head would cause pain. One of them who was much improved three years later said: "I can now waggle my head from side to side without getting it." 2 patients stated that they could usually cough without pain when lying down. 2 others had noticed that on getting up in the morning they could cough without pain but that the liability soon appeared after they had assumed the vertical posture. One remarked that when he coughed if his head was well back the pain

was much less. Another when lying back in a chair bumped the back of his head severely and was thereafter free of the liability for two days. It has already been noted that in one case there was recovery after lumbar puncture, and in another temporary recovery after lumbar puncture, and finally complete recovery after an air encephalogram. These observations, for what they are worth, support the impression gained from the analysis of the cases having a proven cause that the pain is due to stretching of a pain-sensitive structure within the posterior fossa, which may in the benign group be due to an adhesive arachnoiditis.

With regard to the pathogenesis of the lesion there are no significant clues. 18 of the 21 patients were males. The earliest age of onset was 37, the latest 77, with an average age of 55.

A history of possibly relevant head injury was obtained only in one instance (Case 10). In another (Case 9) the previous occurrence of epileptic seizures raises the possibility of trauma. The possibility of an infective factor deserves consideration. One patient had an old-standing bronchiectasis, one had diverticulitis and the onset of his symptoms occurred shortly after colonic lavage. In another case there was a background of recurrent cystitis. In another the onset followed a severe attack of gastro-enteritis. In 2 cases recovery followed the extraction of an infected tooth. In 3 others there was a past history of malaria. A past history of migraine was obtained in 5 cases, which is probably higher than might be expected in a random sample of the population.

Summary

(1) 6 cases are recorded in which transient severe pain in the head on coughing, sneezing, straining at stool, laughing or stooping was for a long time the outstanding or only symptom of organic intracranial disease. These included a posterior fossa meningioma, a cyst of the mid-brain, 3 cases of basilar impression from Paget's disease, and one in which the symptoms developed after removal of an acoustic tumour.

(2) The mechanism of the pain in these cases is discussed in relation to the observations of surgeons operating under local anæsthesia and the phenomena of lumbar puncture headache.

(3) 9 cases are recorded in which the presenting symptom was a similar liability to pain provoked by coughing and the other factors above mentioned; there was no evidence of an organic cause; and the symptom finally disappeared.

(4) In 6 further cases of this type there was substantial improvement at the time of the last observation.

(5) In a further 6 cases with exactly comparable symptoms the evidence against any progressive intracranial disease is presumptive. Two

ultimately died of heart disease without cerebral symptoms. In the remainder no satisfactory follow-up was achieved.

(6) It is concluded that a syndrome of benign cough headache exists.

(7) The available data relevant to the mechanism and pathogenesis of the syndrome are discussed.

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CEREBRAL DOMINANCE IN SINISTRALS

BY

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I. INTRODUCTION

IT has become abundantly clear in recent years that the relationship between handedness and cerebral dominance is far less clear-cut than was formerly supposed. Although the classical rule relating right-handedness and left hemisphere dominance has not been seriously challenged, the position with regard to left-handedness has undergone a complete transformation. No longer can it be accepted that right cerebral dominance is the rule in left-handed individuals or that aphasia resulting from a left-sided lesion in a left-handed patient is in any way exceptional. Indeed two recent surveys of the literature have established that cases in which a left-handed patient owes his aphasia to a lesion of the left hemisphere actually outnumber those in which aphasia has been due to a lesion of the right hemisphere (Goodglass and Quadfasel, 1954; Zangwill, 1955). It would therefore appear that a dissociation between handedness and "brainedness" is far from unusual: Indeed "left-brainedness" might well appear to be the more prevalent form of cerebral organization in left-handed individuals.

A suggestion put forward by several recent authors is that speech in sinistrals is represented bilaterally, i.e. that no firm hemisphere dominance becomes established in these cases. This view, first advanced by Chesher (1936) on the ground that aphasia in persons of mixed handedness is liable to occur with lesions of either hemisphere, has recently gained some support from the findings of Conrad (1949), Subirana (1952) and Humphrey and Zangwill (1952). These findings have been summarized and discussed by Critchley (1953). In principle, Conrad (1949) argues that left-handedness in itself implies imperfect lateralization of the language functions, i.e. a constitutional weakness in cerebral specialization of function. In support of this hypothesis, he adduces not only the fact that aphasia in left-handed patients would appear to occur with approximately equal frequency with left-sided and right-sided lesions but also that minimal or transient dysphasia is extremely common in sinistrals irrespective of the side of the lesion. At the same time, it is important to

bear in mind that statistical analysis of Conrad's findings reveals no significant difference between left- and right-handed patients in respect of transient dysphasias (Goodglass and Quadfasel, 1954). Until a controlled study of the severity and duration of speech disorder in relation to handedness has been carried out, it is difficult to place much weight on this point as evidence for bilateral representation. Further, the not uncommon occurrence of severe and persistent aphasia in left-handed patients with strictly unilateral lesions (Humphrey and Zangwill, 1952) suggests that speech, in some sinistrals at least, is lateralized as fully as in the dextral. Although Goodglass and Quadfasel (1954) make some allowance for these difficulties in their formulation of language laterality in terms of a statistical distribution, it must be borne in mind that no certain evidence for bilateral representation of speech as yet exists.

Impressed by the frequency of aphasia in sinistrals with left-sided cerebral lesions, some recent authors have gone so far as to question the very existence of right hemisphere dominance—even in left-handed patients. Thus Roberts (1956), in a survey of 345 cases (including 33 sinistrals) operated upon by Penfield, claims not to have found a single case of permanent aphasia resulting from a lesion limited to the right hemisphere. Bauer and Wepman (1955) express a similar opinion. None the less, one may point out that a few convincing cases of long-lasting aphasia from right-sided lesions in both sinistrals and dextrals have been reported in the literature (Humphrey and Zangwill, 1952; Ettlinger, Jackson and Zangwill, 1955) and that there are undoubtedly a few cases in which severe and widespread left-sided brain damage in left-handed patients has given rise to no speech disorder whatsoever (Goodglass and Quadfasel, 1954). Taken together, these findings provide strong evidence for the existence of right hemisphere language laterality—in some sinistrals at least. We may, however, agree with Goodglass and Quadfasel (1954) that right hemisphere dominance is very much less common than left-handedness.

Having regard to the "climate of speculation" enveloping issues of cerebral dominance, Critchley (1954) has rightly urged that neurologists clearly require a great deal of further clinico-pathological evidence as to the consequences of unilateral brain disease in left-handed and ambidextrous subjects. Not only are fully reported cases surprisingly rare, but practically no attention has been given to criteria of dominance other than speech and handedness. With these considerations in mind, Critchley (1954) has himself briefly communicated 14 cases of parietal syndromes following unilateral lesions in ambidextrous and left-handed patients. In 12 cases of left-sided lesion, he reports that dysphasia was present in 7 cases (transient or mild in 3), bilateral ideomotor dyspraxia in 3 and constructional apraxia in 1. Further, 5 of these patients (2 without dysphasia) presented a Gerstmann syndrome. In the 2 cases of

right-sided lesion, no dysphasia was apparent in either patient but both gave evidence of constructional apraxia, in one case associated with a minimal spatial loss. In his discussion of these cases, Critchley comments on the fact that sinistrality does not entail a simple mirror reversal of the two hemispheres in regard to cerebral dominance: In consequence, the clinical patterns of breakdown following unilateral lesions in left-handed patients are complex and unpredictable.

A recent study by Hécaen and Ajuriaguerra (1955) yields results broadly comparable to those of Critchley (1954). Their material comprised 11 cases (9 sinistral and 2 reported as ambidextrous). The lesion was left-sided in 5 cases and right-sided in 6. In the 5 cases of left-sided lesion, appreciable dysphasia was present in 4, ideomotor dyspraxia in 1, constructional apraxia in 3 and disorders of the body-scheme in 3. One case of left occipital lobectomy presented a circumscribed alexia without aphasia. In the 6 cases of right-sided lesion, only slight dysphasia (paroxysmal in 4 and transitory in 2) was in evidence. On the other hand, well-marked constructional apraxia was observed in 5 cases and disorders of the body-scheme in 3. These authors comment on the comparative mildness of the speech disorder in their cases irrespective of the laterality of the lesion. In particular, comprehension of speech was almost always found to be intact. They also direct attention to the frequency of dysgnosic and dyspraxic manifestations in the absence of gross defect of expressive speech. In general, Hécaen and Ajuriaguerra conclude that their findings do not suggest that right hemisphere dominance is in any sense constant in individuals of sinistral bent. On the contrary, dominance would appear to be highly variable as between both individuals and functions, and to offer greater possibilities of substitution in the event of unilateral damage to either hemisphere.

In the present paper, we propose to communicate 10 cases in which dysphasia and kindred disturbances were observed in association with unilateral cerebral lesions in left-handed patients. With one exception, all patients were referred to the Psychological Department for routine assessment between 1949 and 1954, and comprise all in whom there was evidence both of left-handedness and of a lesion involving the "language areas" of one or other hemisphere. Special attention has been paid to (*a*) the pattern of lateral preferences; (*b*) familial sinistrality; (*c*) type and severity of speech disorders; and (*d*) presence or absence of dyspraxia and kindred deficits presumed to bear on hemisphere dominance, e.g. the Gerstmann syndrome. Although this series of cases is too small to permit of statistical evaluation, it is felt that a further addition to the sparse literature of cerebral organization in sinistrals may prove of value.

II. Case Reports

The first case is that of a draughtsman, left-handed apart from writing,

who developed a right hemiparesis with severe dysphasia following removal of a large left fronto-temporal meningioma. Whereas the motor disability recovered almost completely, a moderate dysphasia remained in evidence five years after operation. Writing in this patient improved to a notably lesser extent than expressive speech.

Case 1 (N.H. No. 11055).—The patient, aged 43, was admitted with a history of headache and failure of vision in the left eye. On examination, he was found to have some nominal aphasia, bilateral papilledema, V.A.R. 6/36, V.A.L. 6/24, with constricted fields, a right facial weakness, brisker reflexes right than left, and tactile inattention in the right limbs. There was no dyspraxia, disorientation for right and left, or visual agnosia. Ventriculography revealed a large left hemisphere lesion in the fronto-temporal region.

At operation (Mr. Wylie McKissock) a large meningioma was removed (it was thought completely), together with a portion of the left frontal lobe. The point of attachment of the tumour was the pterion and the outer third of the lesser wing of the sphenoid.

Following operation, the patient had a right hemiparesis with marked dysphasia (speech was at first confined to "yes"). These disabilities underwent gradual improvement, residual symptoms on discharge being a moderate mixed dysphasia and some right-sided motor and sensory disability.

On readmission five years later, the patient stated that he had made progressive recovery in all spheres *apart from writing*, which remained severely affected. On neurological examination, the patient's ability to express himself in speech was found to be severely limited and he was also handicapped in reading aloud. Some errors were made in carrying out more complicated oral commands. Principal neurological findings at this time were a lower right facial weakness, slight loss of power in the extensors of the right elbow and abduction of the right shoulder, and impaired execution of fine movements in the right hand. Tone, power and co-ordination normal in the lower limbs. No abnormal sensory findings. No apraxia, agnosia or disorientation for left and right on his own body. body.

On psychological examination, fuller testing revealed that the expressive speech defect predominated over the receptive and that occasional failures occurred in naming objects. Spontaneous writing was severely impaired and displayed marked agrammatism (fig. 1). Although spelling and letter-formation were intact, the

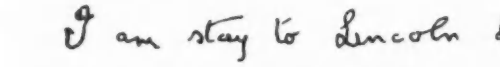


FIG. 1.—Specimen of spontaneous writing in Case 1 (Right-handed writer).

patient's attempts to express himself in writing were virtually incomprehensible. Simple calculation was possible but arithmetic in general was evidently defective. The patient had formerly been proficient in the calculus but now found himself unable to differentiate or integrate numbers. There was some difficulty in silent reading and oral reading was marked by frequent word-substitutions. The patient could copy script or designs extremely well and gave no evidence of a constructional apraxia. Topographical memory was intact. On the Wechsler-Bellevue Scale, the patient was found to have an I.Q. of 79 on the Verbal and of 114 on the Performance Scale. His pre-morbid intelligence level was certainly well above average.

Handedness in this case is of considerable interest. The patient stated that

he had always been strongly left-handed, except for writing, and had always preferred to use his left hand in his work as a draughtsman. He was left-footed but probably right-eye dominant. Inquiry revealed that his father and one of his three siblings were left-handed.

Despite the pronounced sinistrality, both personal and familial, the severity and persistence of the speech disorder in this case strongly suggest that the major hemisphere was the left.

The next 3 cases are of interest in so far as predominantly expressive speech disorders occurred in connexion with anterior cerebral lesions. The lesion was left-sided in the first, right-sided in the second, and bilateral —though predominantly left-sided—in the third.

Case 2[1]—An electrical engineer, aged 34, was admitted complaining of headaches, double vision on looking to the right, noises in the head, and recent deterioration of memory. He had had a number of generalized convulsions with loss of consciousness, the last about a year prior to admission. Following each attack, the patient was aphasic for a few minutes and if he attempted to express himself in writing the result was jumbled and incomprehensible. He had also had some recent attacks of dysphasia without generalized convulsions. In these attacks there was slowing of speech, with stuttering and difficulty in finding words. The patient also reported that he had got the order of words wrong and had indulged in involuntary Spoonerisms. An interesting feature was that he had noticed a marked fall-off in his powers of receiving Morse, which he had learned at the age of 8 years and at which he was highly proficient. His rate had fallen from 18 to 5 words per minute. On the other hand, his powers of sending Morse had apparently not deteriorated. The patient reported occasional slight difficulty in understanding technical information though none in ordinary conversation.

On examination, the main findings were mild bilateral papillœdema, right sixth nerve palsy and facial weakness on right on emotional expression. V.A.R. 6/5, J2. V.A.L. 6/5, J1. Fields full. Some increase in tone of both lower limbs. Reflexes brisk in both upper limbs, much more so in lower limbs, especially the right. No sensory impairment. Speech was observed to be slow and somewhat discursive but without frank dysphasia. The patient showed no obvious defect in comprehension or reading but his writing was mildly dysgraphic. There was no visual-spatial loss.

EEG examinations suggested an expanding lesion in the left frontal or fronto-temporal region. A left carotid angiogram gave evidence of a large space-occupying lesion in the left frontal region.

At operation (Mr. Pennybacker and Mr. Simpson) a large glioma was removed from the left frontal lobe, extending nearly to Broca's area. The resection was subtotal.

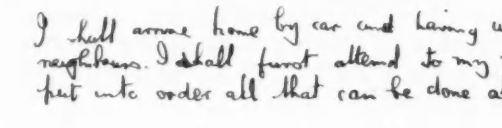
Immediately following operation, the patient had a right facial weakness and mild right hemiparesis. He was also profoundly aphasic. In response to questions, he used only single words, such as "yes," "well" and "very well." He was able to carry out simple requests to order but was unable to protrude his tongue to oral command though could do so spontaneously.

One week later, there was still very little speech and the patient was found

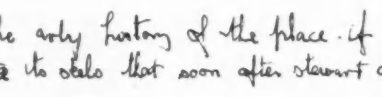
[1]We wish to thank Mr. J. B. Pennybacker, of the Department of Neurological Surgery, Radcliffe Infirmary, Oxford, for his kind permission to study this case and to include it in our series.

to be unable to write his name and address correctly. He could read aloud more adequately than he could speak spontaneously but made some paraphasic errors. The patient could name common objects, do simple additions slowly on paper, and copy designs and circuit diagrams adequately (Dr. Zambellas). His affect was cheerful and unworried.

Two weeks post-operatively, the patient's speech had improved slightly but his writing remained grossly defective (fig. 2).



(a)



(b)

FIG. 2.—Specimens of writing in Case 2 (Left-handed writer): (a) Pre-operative; (b) Two weeks post-operative.

Four weeks post-operatively, the patient's conversation was still very restricted and some errors were made in naming objects. Comprehension of speech was superficially good but errors were made in carrying out complex instructions, especially those involving laterality. Copying and drawing were adequate but spontaneous writing remained much impaired. Reading aloud was hesitant, with absence of normal intonation, and grasp of meaning was apparently not too good. The patient confused his right and left sides but showed no other disorders of the body-scheme. His copying of designs, even quite complex ones, was entirely accurate. There was now hardly any lateralized weakness (Mr. Simpson).

The patient was transferred elsewhere for a course of deep X-ray therapy, which he tolerated well. There appeared to be some improvement in his aphasia though no further change in the objective neurological signs.

On psychological examination six months post-operatively (O. L. Z.), the patient's speech was found to be fluent, although still far from normal. His conversation was hesitant and stumbling, with occasional errors in word-choice and at times somewhat bizarre grammatical constructions. He was unable to explain idioms or proverbs satisfactorily and was markedly discursive. Writing had clearly much improved, though many mistakes were still made in spelling, both oral and written. Reading aloud was fair, with normal comprehension. Complicated oral commands were executed without error. Calculation was fair on paper though very poor mentally. Drawing and construction were found to be little, if at all, affected. No dyspraxia, disorientation for left and right, or finger-agnosia. The patient had noticed considerable recent improvement in his powers of receiving Morse. He was mildly euphoric.

Handedness in this case was distinctly unusual. The patient wrote with his left hand and had always done so. He also threw a ball and played unimanual games left-handed. On the other hand, he cut bread, struck matches, and used penknife or scissors in a preferentially right-handed fashion. He was probably right eye-dominant and had no clear foot-preference. Both the patient, his two

siblings, his wife and their eldest child were right-handed. His second child was still too young to exhibit hand-preference.

The severity and the duration of this patient's dysphasia create a prima facie supposition that the affected (left) hemisphere was the major one. It is noteworthy that the patient, though partially ambidextrous, had always written with the left hand.

The next case will be described more briefly as the full case notes are unfortunately not now available.

Case 3 (N.H. No. 46494).—A labourer, aged 52, left-handed, presented a marked expressive dysphasia due to a right frontal cerebral abscess (secondary to bronchiectasis). On admission, the patient's speech was severely limited but improved fairly rapidly with repeated tapping of the abscess. He could read and execute simple printed commands adequately, though not without difficulty, and there was some paraphasia on tests of naming objects. Writing was grossly impaired and extremely perseverative. Thus when asked to write: "I have had a bit of an operation on my head," the patient wrote: "It hand and aan a bat at at a I bit apoplation." As regards neurological signs, visual fields were full to confrontation; tone and power in the left hand were slightly reduced at first but recovered within three weeks. There was an incomplete left facial palsy.

On psychological examination one month after admission, the patient's speech was found to be practically normal, with only rare errors in naming objects. On the other hand, his writing still showed some disturbance, mainly in spelling and in the order of letters within a word. Thus he wrote "surcafe" for "surface" and "biginging" for "beginning." Oral spelling was less impaired, the errors made appearing to arise on a simple phonetic basis. Reading aloud was somewhat dysarthric, with an occasional verbal omission or substitution. Simple arithmetic was slow but in general accurate. Comprehension of speech was intact.

FIG. 3 (*Case* 3).—Specimen of mirror-writing.

The patient gave no evidence of disorientation for right and left and no finger-agnosia. He could execute Head's "Hand, Eye and Ear" tests without difficulty. Constructional tests were executed predominantly with the left hand and showed no gross deficit. There was no tendency to neglect the left limbs or the left half of extra-personal space. No dyspraxia. Intelligence tests suggested that the original level had been low-grade but that overall deterioration was minimal.

The patient was an unskilled labourer who seldom had occasion to read or write. He left school at fourteen and stated that although he had not been "too good a scholar" he could always write a letter when necessary and undertake simple calculations. He was consistently sinistral for all unimanual activities, apart from writing and drawing, and was also left-footed and left-eyed. An interesting feature was that the patient, when asked to write with the (non-preferred) left hand, invariably produced "mirror-writing" (fig. 3). He knew of no left-handedness in his family.

This is a case of a severe (though transitory) expressive dysphasia and dysgraphia associated with a right anterior cerebral abscess in a left-handed man of relatively poor endowment and education. The patient had always written with his right hand and knew of no left-handedness in his family.

Case 4 (N.H. No. 28280).—A housewife, aged 42, left-handed apart from writing, was admitted with complaints of headaches, weakness of the right arm and leg, and impairment of memory. Three weeks previously she had been admitted to another hospital in status epilepticus and had remained unconscious for twenty-four hours after cessation of the fits. On recovery of consciousness, she was found to have a right hemiplegia but no aphasia. Her hemiplegia improved to some extent but the right leg remained spastic, with markedly diminished power.

On neurological examination, visual fields were full to confrontation. V.A.R. and L. J2 (corrected). Fundi normal. Pupils equal, reacting normally. Eye movements full and equal in all directions. No nystagmus. Minimal right facial weakness. There was a powerful grasp reflex on the right and a lesser one on the left. Slight but definite increase of resistance in the right arm to passive stretch, mild generalized weakness on right and increased resistance in both lower limbs. Bilateral weakness of hip-flexion, much more marked on right. Tapping and fine finger movements slow and clumsy in the right hand. Tendon reflexes brisker on right; left plantar extensor, right equivocal. No gross sensory impairment. No apraxia.

On psychological examination, the patient spoke slowly but gave little evidence of frank dysphasia. At times she misnamed objects, though always corrected her mistakes. The patient could read correctly, though not quite accurately, at times missing out small words or adding a word not present in the text. Writing was slow and stilted, occasional mistakes being made on dictation tests. These errors were not self-corrected. Calculation was impaired. Mild deficit in verbal intelligence tests though visual-spatial and constructional tests were adequately executed.

There were no indications of finger-agnosia, right-left disorientation, or dressing dyspraxia. No spatial agnosia or unilateral visual neglect but definite evidence of right-sided sensory neglect, with incipient hemi-depersonalization. The patient complained that her right side felt as though it did not belong to her, and occasionally as though it were wholly absent.

Ventriculography gave evidence of a left frontal tumour involving the genu of the corpus callosum and extending back into the parietal lobe. A biopsy taken from the left frontal region established its nature as an astrocytoma, Grade III. The patient was discharged elsewhere for deep X-ray therapy.

This is the case of a left-handed woman, right-handed in writing, who showed evidence of a bilateral frontal lesion (predominantly left-sided) with only minimal indications of dysphasia.

The next case is one of a predominantly receptive dysphasia consequent on disease of the left temporal lobe.

Case 5 (N.H. No. 47995).—A company secretary, aged 60, was admitted complaining of difficulty in speech following a convulsive attack two months previously. After this attack, he was said to have been confused for one hour, talking incoherently and apparently unable to grasp what was said to him. Four days later he returned to work, but it was noticed that his speech was faulty, with some misuse of words. The patient's wife reported that he had lost interest in his work and showed recent defects of concentration and memory.

On neurological examination, the patient was found to be severely dysphasic but without signs of dyspraxia, finger-agnosia or specific disorientation for right and left. Visual fields were full to confrontation. Visual acuity J2 both eyes. Fundi normal, apart from some fullness of the veins. Mild right facial weakness. Motor system normal apart from slight weakness of the right arm and very slight impairment of fine movements in the right hand. Tendon reflexes brisker on right: Abdominals present. No abnormal sensory findings.

On psychological examination, the patient's dysphasia was considered to be predominantly receptive and amnesic. Speech was markedly paraphasic, especially on reading aloud. There was gross nominal defect. In writing, the patient made many errors in word-choice and spelling, his spontaneous compositions approximating to jargon. Writing to dictation was even more severely impaired, with a profusion of paraphasic errors. Comprehension of speech was slightly, though definitely, impaired, leading to slowness and failure in executing oral commands. Reading was likewise defective, the patient often being at a loss for the meaning of a word which he could enunciate correctly. He could follow simple arithmetical procedures but made many errors on tests of calculation. Verbal intelligence was impaired.

Apart from dysphasia, this patient's disabilities were comparatively slight. He gave no evidence of visual agnosia, colour agnosia or constructional apraxia. Kohs block designs were copied without gross deficit. No dressing dyspraxia. Topographical memory, as judged by maps and plans, was thought to be intact. He was able to solve the Weigl sorting test, though his performance was hesitant and slow.

Ventriculography gave evidence of a left temporal lobe glioma, confirmed by a biopsy taken from this region. There was significant deterioration following this procedure with exacerbation of the jargon aphasia and the patient was transferred elsewhere for a course of deep X-ray therapy.

This patient was consistently left-handed on unimanual tasks (apart from writing) and was also left-footed. He knew of no left-handedness in his family.

The next 3 cases are of interest in so far as all presented features ordinarily ascribed to involvement of the major parietal lobe. Dysphasia was present in 2.

Case 6 (N.H. No. 44435).—An actor, aged 58, was admitted complaining of numbness and weakness of the right hand, and attacks of twitching in the right face and hand of recent onset.

On neurological examination, spontaneous speech was slightly indistinct but otherwise adequate. Reading and comprehension appeared to be intact but writing and calculation were severely affected. The principal neurological findings were: V.A.R. 6/9; V.A.L. 6/9. Fields full to confrontation. Bilateral papillœdema, more marked on the left. Pupils equal, reacting briskly to light and on convergence. External ocular movements full. Severe right facial weakness present on voluntary movement. Slight wasting and moderate weakness of the right arm and minimal weakness of hip flexion on the right. Tone normal in arms and legs. Right plantar response extensor. Light touch and pain sensation normal but postural sense impaired in the right arm to the elbow and in the right toes. No inattention to touch over the right side but stereognosis and 2-point discrimination impaired in the right hand. No apraxia, finger-agnosia or disorientation for right and left.

Psychological examination revealed that the patient was able to write his name with the left hand (previously he had written with the right) and it is noteworthy that this handwriting was of good quality. He could write short sentences but with much omission and mispelling of words. Formation of letters, however, was adequate. Calculation was severly affected, the patient having apparently lost the concept of division. Drawing, copying and simple constructional tasks were executed without gross defect. Topographical memory was probably intact.

One week later, there was evidence of variable tactile inattention over the right hand, with incipient hemi-depersonalization. When the patient's right hand was rubbed, he said. "It's as if it's someone else you're touching and not me—and yet I know it's me. It's uncanny." There was also evidence of episodic ideational dyspraxia.

Arteriography revealed a space-occupying lesion in the left hemisphere, probably in the posterior parieto-temporal region. Following ventriculography, a left parietal craniotomy was performed and a biopsy taken from this region established its nature as an astrocytoma, Grade IV.

After operation, the patient's speech remained relatively normal but he was occasionally at a loss for a word. Some impairment in reading was now noticed. There was severe ideational dyspraxia. On psychological examination, he was found to have a slight defect in naming objects, complete agraphia (being unable even to print his name), acalculia, and some left-right disorientation. He was discharged elsewhere for X-ray treatment but readmitted three weeks later for re-examination. It was found that speech had further deteriorated and that there was now marked difficulty in word-finding, a low-grade oral comprehension defect, slow and inaccurate reading, agraphia, acalculia and incipient autotopagnosia. There was also a perceptible finger-agnosia.

It was established that this patient was left-handed for throwing, cutting and use of tools in general. As a child he had begun to write with the left hand but had been forced at school to use the right. He knew of no left-handedness in his immediate family.

The case described above is of interest in that a well-developed parietal lobe syndrome, comprising dysphasia, dyspraxia, hemi-depersonalization and a Gerstmann syndrome, presented from a left temporo-parietal tumour in a left-handed man. The following case is very similar and will

be described more briefly as a full account is available elsewhere (Zangwill, 1954).

Case 7 (N.H. No. 19803).—This is the case of a clerk, aged 42, left-handed apart from writing, who presented a mild dysphasia, predominantly receptive and semantic, due to a glioma involving the left posterior parietal region. There was severe dysgraphia, marked by constant literal errors, dyscalculia, some right-left disorientation, together with constructional, dressing and doubtful ideomotor dyspraxia. No unilateral neglect, visual or sensory, and no disorder of spatial orientation. Intellectual level was high-grade without appreciable overall deterioration. There were no ascertainable sinistral familial antecedents.

The next case is of exceptional interest in so far as the patient presented a well-marked left parietal syndrome without the least trace of dysphasia. This case has already been briefly communicated by Critchley (1954).

Case 8 (N.H. No. 43335).—An agent, aged 53, was admitted complaining of weakness of the right arm and leg and a history of several attacks of sudden stiffness in the right leg which spread in later attacks to the right arm and face.

On neurological examination, the main findings were doubtful early bilateral papillœdema, slight right lower facial weakness, severe right spastic hemiplegia, more marked in the leg than in the arm and face, increased reflexes on right and right plantar response extensor. There was some inattention to light touch over the right side of the body with impairment of vibration sense, two-point discrimination and postural sense in the right arm and leg. Visual fields were full and there was no dysarthria or dysphasia.

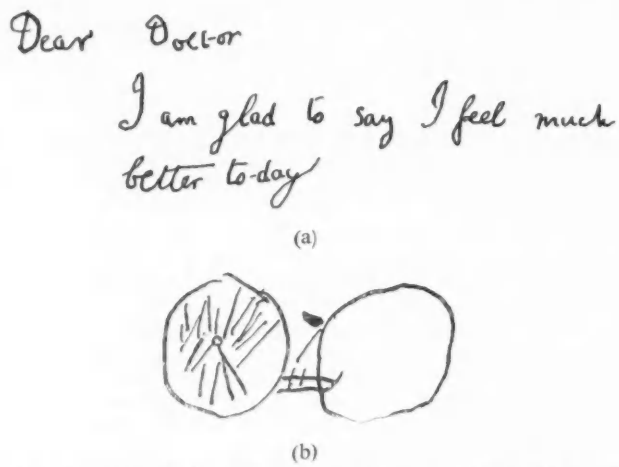
Ventriculography revealed depression of the roof of the left lateral ventricle, suggestive of a left-sided parasagittal space-occupying lesion. A biopsy taken from the left posterior parietal region was reported as having the features of an astrocytoma, Grade III.

The patient was discharged elsewhere for a course of deep X-ray therapy, which resulted in gradual improvement of the hemiplegia and the patient's temporary return to active life. He was however readmitted six months later complaining of headaches and difficulty in control of the right arm and leg.

On neurological examination, fundi were normal and visual fields full to confrontation. Moderate right facial weakness. Voluntary movements of the right arm were found to be occasionally associated with a coarse irregular tremor of the elbow. Slight generalized muscular wasting and moderately severe weakness and increase in tone of the right limbs. Reflexes brisker on right; right plantar response extensor. Some inattention to touch (though not to pinprick) over the right half of the body. Position sense normal at fingers but markedly impaired in right foot. Vibration sense slightly impaired on right side and two-point discrimination reduced in right fingers. No dysphasia.

On psychological examination, no evidence of dysphasia could be elicited either at interview or on special tests. The patient's speech was fluent and he even composed a poem describing his business! Object naming was fully intact. Reading aloud was a little slow and he took time to appreciate the exact meaning of a sentence or to draw inferences from it. It is doubtful, however, whether this could properly be termed a semantic aphasia. He was able to write fairly adequately with the (affected) right hand and his script was in no way dysgraphic. He was able to copy designs adequately, though drawing from memory was exceedingly poor (fig. 4). Performance on block-design tests was poor, with some tendency to "close in" to the model, but without neglect of one side of the model

or the reproduction. The patient drew an adequate map of England, marking in compass directions correctly. No loss of orientation in familiar settings was reported but he had real difficulty in following or describing routes within the hospital. There was also evidence of a minimal loss of topographical memory. Vocabulary score was 1.0 S.D. above mean, indicating high-average premorbid intelligence level.



(a)

(b)

FIG. 4 (*Case* 8).—Dissociation of language and praxis: (a) Specimen of writing; (b) Bicycle drawn from memory.

In the following weeks, the patient developed signs of mild bilateral ideomotor dyspraxia, disorientation for right and left (both on himself and the examiner), a mild, though definite, finger-agnosia, particularly marked when he was asked to handle a pair of gloves, but without the least trace of aphasia, agraphia or acalculia (Dr. MacDonald Critchley).

This was a strongly left-handed man who had been converted to right-handed writing and drawing at the age of 5. He used all tools left-handed, kicked with his left foot and used a spade in sinistral fashion. In boxing, he relied on his left punch. He was probably right eye-dominant. He knew of no left-handedness in his family.

A striking finding in Case 8 is the development of bilateral dyspraxia, right-left disorientation and finger-agnosia, without agraphia, acalculia or nominal aphasia. It may therefore be inferred that whereas praxis and topognosis were represented on the left side, as in dextrals, all language functions were represented in the right hemisphere.

The last two cases are essentially negative: In Case 9, a right parietal lesion in a left-handed man gave rise to unilateral visual neglect and constructional disability accompanied by a minimal grade of dysphasia. In Case 10, a left temporo-parietal neoplasm in a left-handed boy produced no psychological deficit apart from a questionable nominal defect.

Case 9 (N.H. No. 45593).—A clerk, aged 57, left-handed apart from writing, was admitted complaining of headaches and motor disability of the left hand and foot. His wife reported that he had found difficulty with his work over the past year.

On neurological examination, visual acuity was found to be J6 in both eyes. Left homonymous hemianopia to confrontation and moderate bilateral papillœdema with hæmorrhages and exudate. Except for slight weakness of flexion at the left hip and knee and of dorsiflexion of the left ankle, power normal in all limbs and no increase of tone. Tendon reflexes exaggerated on the left; left plantar response extensor. Touch and pain sensation unaffected but well-marked inattention to bilateral simultaneous stimulation over the left side, particularly in the lower limbs. Joint position sense and two-point discrimination defective in left fingers and toes. No dysarthria, dysphasia or dyspraxia.

On psychological examination, no speech disorder could be established apart from a very occasional mistake on object-naming tests. The patient stated that he was now and again at a loss for a word, but no instance of this was recorded at interview. Comprehension of speech and reading were fully intact. Writing with the right (preferred) hand was adequate, though slow, with a questionable defect of spelling. No dyscalculia. Verbal intelligence tests were adequately solved.

In the visual-constructive sphere there was evidence of moderate disability. Designs were very poorly copied and there was a tendency to neglect the left-hand side of the drawing. Block-design performance was much impaired. In writing, the patient had great difficulty in maintaining proper orientation of the lines on the paper. He was prone to miss doors and turnings on his left-hand side and to leave food on the left-hand side of his plate. There was also a history of episodic failure to recognize his own house. No finger-agnosia, dressing dyspraxia or disorientation for left and right on his own body.

He was left-handed (apart from writing), left-footed and left eye-dominant.

The EEG gave evidence of continuous slow activity throughout the right side and two foci, one low down in the frontal region and the other in the posterior parietal region, could be recognized. The left side was within normal limits.

Ventriculography gave evidence of a right parietal secondary carcinoma, verified by a biopsy taken from the posterior parietal region.

This patient displayed what is essentially a minor parietal syndrome (McFie, Piercy and Zangwill, 1950). Dysphasia was minimal, even questionable. The absence of dyspraxia, dyslexia, and all elements of the Gerstmann syndrome suggests that the major hemisphere was almost certainly the left.

Case 10 (N.H. No. 6221).—A strongly left-handed boy, aged 15, was admitted complaining of headaches and attacks of pins and needles in the right hand. There was a history of epilepsy of recent onset.

On neurological examination, the main findings were bilateral papillœdema, a rapid and sustained nystagmus on gaze to the right, marked lower right facial weakness, increase of tone in the right arm and loss of associated movements of the right arm in walking. No dysphasia, but a mild slurring dysarthria. It was reported by the patient's mother that the boy did not speak quite normally for some minutes after an attack, appearing to have difficulty in expressing himself.

On psychological examination, test findings indicated that premorbid intelligence was almost certainly low-grade. No signs of dysphasia could be elicited apart from a questionable nominal defect for more unusual objects. No impairment of

comprehension. Reading, writing and calculation were poor but probably not significantly below the overall scholastic level and presented no specifically dysphasic signs. No visual-spatial, topographical or constructional deficits.

Electroencephalography suggested a left temporo-parietal lesion, confirmed by ventriculography. A left temporal craniotomy disclosed a large cyst with associated tumour, whose nature was established at biopsy as an astrocytoma with malignant de-differentiation.

Inquiry revealed that the boy was left-handed for all unimanual activities, including writing and drawing, and was also left-footed. His mother and one brother were likewise left-handed; his father, two other brothers and all four grandparents were however right-handed.

The patient died four years after discharge but no post-mortem examination was made.

This is the case of a left-handed boy, with some familial sinistrality, who developed a slurring dysarthria with questionable nominal dysphasia in association with a malignant left temporo-parietal neoplasm. There was no interference with reading, writing, calculation or understanding of speech. Intellectual level was low-grade.

III. Analysis of Cases

(1) *Lateral preferences.*—All patients in this group were self-styled left-handers, though all but 2 (Cases 2 and 10) habitually wrote with the right hand. In certain cases, evidence of early conversion to the use of the right hand in writing was forthcoming. The salient data regarding sinistral antecedents and personal preferences are summarized in Table I.

Table I.—Lateral Preference Patterns

	Sinistral	*Lateral preferences*		
Cases	*antecedents*	*Hand*	*Foot*	*Eye*
1	Father and one sibling left	Left, apart from writing; drawing left	Left	? Right
2	None	Left, including writing; partially ambidextrous	Either	? Right
3	None	Left, except writing and drawing	Left	Left
4	Unknown	Left, apart from writing	Unknown	Unknown
5	None	Left, apart from writing	Left	Unknown
6	None	Left, early conversion to right-handed writing	Left	Unknown
7	None	Left, except for writing; partially ambidextrous	Left	Right
8	None	Strongly left, early conversion to right-handed writing	Left	? Right
9	None	Left, apart from writing	Left	Left
10	Mother and one brother left	Strongly left, including writing	Left	Uncertain

It will be seen first that familial sinistrality was ascertained in only two cases (Cases 1 and 10); and secondly, that consistently sinistral hand, foot and eye preferences occurred only in two cases (Cases 3 and 9).

(2) *Dysphasia.*—With one exception (Case 8), some evidence of *speech disorder* was elicited in all cases. This was severe in 4 (Cases 1, 2, 3 and 5), and mild or minimal in the remainder. The form of speech disorder was predominantly expressive in 3 cases (Cases 2, 3 and 4), predominantly receptive in 2 (Cases 5 and 7) and mixed expressive-receptive in 1 (Case 1). In the remaining cases, such dysphasia as was present was mainly restricted to mild defects in word-finding.

Disorders of writing were particularly marked in Cases 1, 6 and 7 (all right-handed writers) and in Case 2 (a left-handed writer). In Case 1, dysgraphia was rather more severe and persistent than the concomitant dysphasia; in Case 7, severe dysgraphia was in evidence despite little or no expressive speech defect.

Disorders of calculation were noted especially in Cases 1, 2, 5, 6 and 7. In the last two cases, the dyscalculia presented as a component of a Gerstmann syndrome.

Disorders of reading were not prominent in this series and no patient presented a circumscribed alexia.

(3) *Parietal syndromes.*—Involvement of the parietal lobe was indicated in 6 cases, 5 left-sided and 1 right-sided. Of the 5 cases with left parietal lesions, evidence of bilateral motor apraxia was elicited in 3 (Cases 6, 7 and 8), right-sided hemi-depersonalization in 2 (Cases 4 and 6), constructional apraxia in 3 (Cases 7 and 9, less certainly in Case 8), and a Gerstmann syndrome in 3 (Cases 6, 7 and 8). In Case 8, the linguistic components of this syndrome were absent. Evidence of dressing dyspraxia was forthcoming in Case 7.

The sole instance of a right parietal lesion in this series (Case 9) presented unilateral tactile and visual neglect associated with moderate visual-constructive loss. There was no dyspraxia, finger-agnosia, dyscalculia, dressing disability or topographical loss and dysphasia was minimal.

(4) *Cerebral dominance.*—The conventional criteria of hemisphere dominance (other than handedness) are (1) severe and relatively persistent dysphasia; (2) dysgraphia; (3) bilateral dyspraxia; and (4) the presence of specific parietal signs, in particular the Gerstmann syndrome. With these criteria in mind, the principal findings in these series of cases have been assembled in Table II. Analysis of the data suggests that left hemisphere dominance for all major functions can be inferred with some confidence in 5 cases (Cases 1, 2, 5, 6 and 7), and less certainly in 2 (Cases 4 and 9). Right hemisphere dominance, or at least right hemisphere language representation, can be inferred, if tentatively, in 2 cases (Cases 3 and 10). In Case 8, there was evidence of right dominance for language but left dominance for praxis and topognosis, i.e. "crossed" dominance.

IV. Discussion

The main findings in this series of cases are (1) the incidence of severe dysphasic syndromes in 5 out of the 10 cases; (2) the clear predominance of

TABLE II.—PROBABLE CEREBRAL DOMINANCE IN TEN SINISTRAL PATIENTS

			Criteria of dominance				
Case	*Lesion*	*Verification*	*Dysphasia*	*Dysgraphia*	*Dyspraxia*	*Gerstmann syndrome*	*Presumptive hemisphere dominance*
1	L. fronto-temporal meningioma	Operation	Expressive-receptive, persistent	Severe, persistent	None	Absent	Left
2	L. frontal glioma; excision	Operation	Expressive; persistent	Moderate	Bucco-lingual	Absent	Left
3	R. frontal abscess	Operation	Expressive, transient	Severe, transient	None	Absent	Right, or indeterminate
4	L. fronto-parietal astrocytoma	Biopsy	Expressive, minimal	Minimal	None	Absent	Left, or indeterminate
5	L. temporal glioma	Biopsy	Receptive, moderate	Moderate	None	Absent	Left
6	L. temporo-parietal glioma	Biopsy	Nominal, mild	Severe	Ideational	Present	Left
7	L. posterior parietal glioma	Biopsy	Receptive, mild	Severe	Ideomotor, constructional and dressing	Present	Left
8	L. parietal astrocytoma	Biopsy	None	None	Ideomotor, constructional	Finger-agnosia and R-L disorientation	Right, for language Left, for praxis and topognosis
9	R. parietal cystic carcinoma	Biopsy	Nominal, minimal	? Minimal	Constructional	Absent	Left, or indeterminate
10	L. fronto-temporal astrocytoma	Operation	? Nominal, minimal; mild slurring dysarthria	None	None	Absent	Right, or indeterminate

speech disorders associated with left-sided lesions; and (3) the absence of any case of persistent dysphasia due to a right-sided lesion. It would therefore appear that "left-brainedness" is the more usual form of cerebral organization in this series of sinistrals.

It is of some interest to note that the various indicators of hemisphere dominance (other than handedness) were relatively consistent. Thus 2 of the 5 patients with involvement of the left parietal lobe presented a bilateral dyspraxia and elements of the Gerstmann syndrome in addition to mild dysphasia. Equally, the sole case of right parietal lesion in this series gave evidence neither of appreciable dysphasia nor of any of the non-verbal deficits conventionally ascribed to lesions of the major hemisphere. Indeed this patient gave the picture of visual-spatial loss of the type regularly found in connexion with posterior lesions of the minor hemisphere in right-handed patients (McFie, Piercy and Zangwill, 1950). At the same time, it is important to bear in mind that one patient with a left-sided lesion (Case 8) presented severe disorders in the sphere of praxis and the body-scheme without the least trace of dysphasia. This observation furnishes a good illustration of Russell Brain's principle of selective dissociation of cerebral functions in relation to dominance (Brain, 1941).

Disorders of writing were well-marked in several of the patients and did not appear to bear any close or essential relation to the preferred writing hand. Thus Case 2 (a left-handed writer) showed severe and persistent defects in written expression following removal of a left frontal glioma. Again, Case 3 (a right-handed writer) showed severe expressive dysgraphia associated with a right frontal abscess. At the same time, there was some evidence that disturbances in writing were more severe (Case 7) or more persistent (Case 1) in patients who had sustained lesions of the hemisphere contralateral to the preferred writing hand.

It is appropriate to inquire whether our findings throw light on the hypothesis of bilateral language representation in sinistrals, particularly in the form in which it has recently been advanced by Goodglass and Quadfasel (1954). Broadly, these authors suggest that "cerebral ambilaterality" is the rule in sinistrals, i.e. that speech is represented bilaterally and some aphasia in consequence liable to accompany lesions of either hemisphere. It is further suggested that extreme "right-brainedness" (i.e. aphasia from right-sided lesions only) and extreme "left-brainedness" (i.e. aphasia from left-sided lesions only) represent opposite extremes of the laterality distribution and are hence to be regarded as exceptional. Now on this hypothesis we should expect first, that aphasia would result with approximately equal frequency from lesions of either hemisphere—as maintained by Conrad (1949); and secondly, that the speech disorder in sinistrals would in general tend to be less severe and persistent than in dextrals. The first expectation is clearly not borne out by our present

findings. Although the predominance of left hemisphere lesions in our material may well reflect an artefact of selection, the comparative infrequency of aphasia in sinistrals with right-sided lesions has been reported too often to be dismissed as fortuitous (Roberts, 1956; Bauer and Wepman, 1955). Although further evidence is needed, it would appear permissible to conclude that aphasia in sinistrals is very much more frequent with lesions of the left than of the right cerebral hemisphere.

As regards severity and persistence of dysphasia in left-handed patients, it is certainly true that the speech disorder was minimal in 3 of our cases and transitory in one. In these 4 cases, the possibility of bilateral speech representation can be seriously entertained. At the same time, it must not be forgotten that the language disturbance in at least 4 of our cases (and probably in five) was entirely comparable in kind and severity to that typically encountered in right-handed patients. In Case 1, indeed, appreciable dysphasia and disabling dysgraphia remained in evidence on examination five years after operation. This patient was not only strongly left-handed himself but had a family history of sinistrality. Further, in Case 8 no dysphasia whatsoever could be ascertained, indicating that language was wholly represented in the unaffected hemisphere. Taken together, these findings hardly lead one to suppose that bilateral representation of speech is the rule in left-handed individuals. One may conclude that language, in a fair proportion of sinistrals at least, is lateralized as completely as in the average dextral.

It may be suggested that the findings in the series of personal cases reported by Goodglass and Quadfasel (1954) do not wholly bear out the authors' own contentions. Of their 13 cases, severe and persistent aphasias were reported in 4, transitory dysphasias in 6 and absence of speech disorder in 3. Taking both positive and negative cases into account, it would appear that speech was fully lateralized in just over half the total cases. These findings, taken together with our own, are not easy to reconcile with the hypothetical distribution of language laterality in sinistrals which Goodglass and Quadfasel (1954, fig. 2) present. One may suggest that the distribution curve given for sinistrals should be skewed to the left in such a manner as to resemble more closely that given for dextrals. This would imply that speech is fully lateralized to the left in the majority of sinistrals and that cases presenting aphasia from exclusively left-sided lesions are in consequence more numerous than those liable to develop aphasia from a lesion of either hemisphere. We would however agree with Goodglass and Quadfasel that extreme "right-brainedness" is a distinctly unusual condition. In conclusion, we would suggest that whereas "cerebral ambilaterality" may well occur in a certain proportion of cases, unilateral representation of speech (usually left but occasionally right) is the most prevalent form of cerebral organization in sinistrals.

V. Summary

(1) The problem of cerebral dominance in sinistrals is briefly reviewed in the light of recent studies.

(2) 10 cases of exclusively or predominantly unilateral brain disease in left-handed patients are reported and the findings analysed in full. The lesion was left-sided in 8 cases and right-sided in 2.

(3) Outspoken dysphasic syndromes occurred in 3 cases with left-sided lesions and in one case with a right-sided lesion. In the latter the speech disorder was transitory. One patient with a left-sided lesion showed severe dysgraphia and constructional defects with minimal dysphasia. Minimal dysphasic signs were elicited in 4 cases, 3 with left-sided lesions and 1 with a right-sided lesion. In one case of left-sided lesion there was no speech disorder whatsoever.

(4) Disorders of praxis and the body-scheme were present in 3 patients with involvement of the left parietal lobe. One patient with a right parietal lesion presented signs of unilateral neglect and visuo-constructive disorder without appreciable dysphasia.

(5) Analysis of the findings indicates consistent left hemisphere dominance for all major functions in 5 cases and probable left hemisphere dominance in 2. Right hemisphere dominance is indicated, if less certainly, in 2 cases. In one case, there was evidence of left hemisphere dominance for praxis and topognosis and right hemisphere dominance for language processes.

(6) The findings are discussed with special reference to the hypothesis of bilateral speech representation in left-handed individuals. It is concluded that whereas some degree of "cerebral ambilaterality" may exist in a certain proportion of cases, unilateral representation of speech (usually left but occasionally right) is the most prevalent form of cerebral organization in sinistrals.

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DISORDERS OF LAUGHTER DUE TO BRAIN LESIONS [1]

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We know very little about the physiology of normal laughter. We are still ignorant of how facial expressions in smiling are mediated, whether by cortical or subcortical structures. Cortical and mid-brain tracts connected with the nervous control of respiration and probably important in laughter, are known to exist, but their relationship to emotional expression is disputable. The neurological mechanisms underlying the emotional states of mirth or joy which usually accompany natural laughter are even less understood. Philosophers, psychologists and neurologists have tried to explain in the language of their individual disciplines how we come to " see a joke " or make a witty remark.

Recent discoveries relating to the anatomy and physiology of the thalamus, hypothalamus, their cortical connexions and their relationships with the limbic structures of the temporal lobe, suggest that a review of the facts concerning disordered laughter resulting from focal cerebral lesions may not be inopportune.

Disordered laughter (or disordered weeping) from brain damage is a clinical curiosity except in cases of pseudo-bulbar palsy due to cerebral vascular disease, or certain cases of advanced multiple sclerosis. In such cases we usually find during life bilateral extensor plantar responses, and at autopsy evidences of bilateral degeneration of cortico-hypothalamic and cortico-bulbar tracts. Disordered laughter, however, also occurs with discrete single brain lesions. This has been less generally recognized. In certain rare cases of epilepsy disordered laughter may occur during part of the fit. In gross lesions involving fronto-hypothalamic connexions the disordered laughter appears to be the result of an excited emotional state.

Normal Laughter and Smiling

Natural laughter may be considered as consisting of two components: (1) the more voluntary phenomena of facial expression in smiling, and (2) the more automatic laryngeal and respiratory phenomena in laughing. Expressed in another way we may say that the emotional expression which

[1]Presidential Address, Neurological Section, Royal Society of Medicine, London; read October 6, 1955.

we call laughter consists of facial movements and a respiratory state in which rhythmic clonic expirations produce phonation. This implies activity of both somatic and autonomic functions. Not only is respiration (normally under chemical control) altered in rhythm, but there may be rise of pulse-rate, flushing and evidences of the outpourings of internal and external secretions.

The subjective *emotional state* of which laughter is the expression is usually, but not invariably, one of amusement or joy. The stimulus arousing the amusement may proceed from our thoughts, but more commonly it comes through visual, auditory, cutaneous (tickling), or other afferent pathways. The laughter response is proportional to the stimulus in degree and duration, and to the feeling of amusement which accompanies the act.

It is difficult to explain the existence of human smiling and laughter with their autonomic accompaniments unless they have to do with a necessity in man to communicate his feelings to others. Animals show their emotions or reactions to a situation by noises or gestures inadequate for us. In man, expressive and emotional movements of the face, as in smiling, act more or less automatically as gestures of speech, reinforcing, giving emphasis, vividness and energy to conversation, quickening attention and sympathy and conveying shades of meaning not otherwise expressed.

In conversational speech, alterations in tonus of the laryngeal musculature together with respiratory adjustments give rise to vocal inflections. Such emotional sounds, expressed whether with or independently of language, signify reactions to our internal emotional state. They occur in animated propositional speech, and in emotional interjections.

The *bulbar automatisms* of laughter are respiratory phenomena adapted to the display of emotional feeling. The fact that they are normally induced by a pleasant emotion gives them a neurological status higher than that of other respiratory automatisms, such as coughing, hiccough and choking. Yawning is probably in an intermediate position having regard to its association with boredom. In the Jacksonian sense the bulbar automatisms of laughter seem to be represented at the highest level as well as at the lowest.

Definitions of Pathological Laughter

The laughter which we meet in focal cerebral disease never resembles natural laughter. Either the sounds or facial expressions are intrinsically different, or else the emotion behind the laughter is absent, or so disordered as to render the sounds inappropriate, contradictory or purposeless.

This study is largely confined to disorders of the emotional expression of laughter. The term "*pathological laughter*" is usually restricted to conditions where the facio-respiratory mechanism is out of control as

the result of focal brain disease or epilepsy. In this condition involuntary spasmodic attacks, superficially resembling the motor manifestations of natural laughter, occur without appropriate emotional feeling. Such attacks are uncontrollable and prolonged and may change from laughter to weeping. Disordered laughter, however, may arise when hypothalamic as well as bulbar mechanisms are acting involuntarily.

In *emotional liability* or *emotional incontinence* the patient gives one the impression at first sight that he is the subject of an ever-altering affective state which is continually playing upon his laughter mechanism. This may be so, but in most cases these manifestations seem to the observer to be unaccompanied by those changes in emotional feeling which the patient seems to express. Patients have great difficulty in making introspective analyses of their laughter-spells. Most pseudo-bulbar cases will admit that it is mirthless. Others seem to feel amusement in some degree as the laughter-spell develops.

The exaggeration of the motor responses of excessive laughter calls to mind Henry Head's description of the exaggeration and persistence of the sensory response in lesions of the thalamus: "It is as if a spark fired the magazine and the consequences were not commensurate with the cause."

Two other adjectives are sometimes applied to pathological laughter—"inappropriate", "contradictory." These imply some alteration either positive or negative in the emotion itself; but not necessarily so, for the normal feeling may be there whilst the patient is incapable of expressing it except by sounds resembling those of uncontrollable laughter. Amongst the criteria of pathological laughter I would place high the lability of the response—how it may change to sobbing or wailing even in the middle of a burst that began as laughter. In the more exaggerated reactions it may be exceedingly difficult to tell from the expression on the patient's face whether he is laughing or weeping. The upper part of the face may seem to express anguish or woe and the lower part laughter. In the slighter reactions there is usually no doubt as to the type of facial response.

Neurological Surveys and Theories

The earliest clinical studies were those of Oppenheim and Siemerling (1886), Nothnagel (1889) and Brissaud (1895). In 1912 Charles K. Mills wrote on "The Cerebral Mechanism of Emotional Expression."

S. A. Kinnier Wilson's paper (1924) on "Pathological Laughing and Crying" is probably the one which most of us here would take as a basis of approach to this subject. Kinnier Wilson pointed out that pathological laughter and crying are allowed by lesions of the voluntary paths of the motor cortex, or by any state in which they exert imperfect control. He postulated a centre linking the seventh nerve nucleus in the pons with the motor nucleus of the tenth (nucleus ambiguus) in the medulla, and the

phrenic nuclei in the upper cervical cord. "By all analogies," he wrote, "this centre must be supranuclear: for the sake of argument we may suppose it has an upper pontine site." This hypothetical facio-respiratory "centre" was, he considered, under double control: (1) *voluntary* through the cortico-bulbar part of the pyramidal tract, and (2) *involuntary* through two of the four respiratory tracts which Walter Spencer (1894) had demonstrated in monkeys' brains on the basis of stimulation experiments. These tracts were said to arise in the posterior orbital gyrus and to descend to the bulb, converging near the mid-line in the subthalamic region and tegmentum. They had both accelerator and depressor functions and thus fitted into Wilson's theory very neatly, for he could in this way explain the mainly expiratory character of laughter and the mainly inspiratory character of weeping.

Charles Davison and Harold Kelman (1939) in their paper "Pathologic Laughing and Crying" dealt not only with the disorders of laughter pathways, but also with their attendant emotional disorders. Many of their cases were single lesions. From a series of 53 cases with 33 autopsies (6 tumours) they concluded that the hypothalamic or some other of the diencephalic nuclei under cortical control were the main centres for the release of affective responses. They considered that the thalamic nuclei, striatum and pallidum might also act as centres for the production of affective responses. Possibly separate pathways or centres existed in intimate connexion with the hypothalamus and the facio-respiratory nuclei in the mesencephalon and metencephalon.

I think that Foerster and Gagel (1933) were amongst the first neurosurgeons to stress the importance of the hypothalamus in the production of states of excitement with laughter and manic speech; although states of excitement and apathy in hypothalamic tumours had been observed previously by Cushing (1912) and by Fulton and Bailey (1929).

Purdon Martin (1950) wrote on "Fits of Laughter (Sham Mirth) in Organic Cerebral Disease." He considered that the evidence adduced from personal and other cases gave practical support to the view that a motor "centre" for laughter is situated in or near the hypothalamus. He emphasized that the "centre" which discharges in these cases was a motor centre and not one exciting emotion.

I shall describe various clinical manifestations of disordered laughter. I propose to show that focal lesions in widespread areas of the brain can cause disturbances of emotion and of laughter at different levels. Focal lesions in the pre-frontal and frontal, temporal and limbic lobes may cause disturbances of laughter, particularly if they lie near the mid-line in the neighbourhood of the hypothalamus and third ventricle. Involvement of both hemispheres or cortical tracts converging towards the mid-line is usual, but not invariable. I shall discuss laughter as an epileptic symptom and its relationship to temporal lobe epilepsy.

Material

In order that the localizing value of the lesion or lesions might be assessed, cases due to single lesions were sought. The clinical records of 20 cases of uncomplicated bulbar palsy due to motor neurone disease, where the lesions are believed to be confined to the motor system (one with autopsy) were studied. The single lesions were tumour cases with autopsy from the literature, and two personal cases with autopsy. Personally observed cases of epilepsy, where the fits appeared as bouts of laughter are quoted and one personally observed case of prolonged laughter culminating in hemiplegia. It is upon the study of isolated focal lesions that this paper is chiefly based, e.g. tumours, aneurysms.

It is to be emphasized that disorders of laughter are more commonly due to diffuse lesions such as arteriosclerosis, multiple sclerosis, encephalitis (lethargic, syphilitic), dystonia musculorum, hepato-lenticular degeneration and severe, diffuse head injury; but as these diffuse lesions are of little localizing value attention has been paid to rarer more discrete lesions.

Clinical Manifestations of Disordered Laughter

The clinical classification of laughter disorders is fraught with dangers and difficulties. Automatic bulbar sounds of laughter may arouse in the patient some emotional feeling as a secondary manifestation. This feeling is sometimes embarrassment; it may, however, be amusement. When the appropriate emotional feeling should be anger or grief, the patient laughs. In many cases emotional feeling is absent during these spells. Spells of prolonged laughter lasting hours or days may occur culminating in hemiplegia, stupor or dementia. Fits of laughter may occur as an epileptic phenomenon.

It is difficult to make a clear line of distinction between such cases and disorders of laughter which arise as the result of emotional excitement (e.g. euphoria) or from loss of volitional control (e.g. confusion, dementia). In this connexion we may recall the observation of Gowers regarding natural laughter. "The will is needed," he said, "not to effect it, but to restrain it."

I shall describe (1) Involuntary and explosive laughter in pseudo-bulbar and bulbar syndromes; (2) Fits of laughter as an epileptic phenomenon (including "ictus ridenti"); (3) Disorders of laughter consequent upon excitement, euphoria and other mental changes.

Disorders of smiling demand separate consideration.

(1) *Involuntary and Explosive Laughter in Pseudo-bulbar and Bulbar Syndromes*

In the spastic explosive laughter of pseudo-bulbar and bulbar palsy the facial and the bulbar muscles have imposed upon them the effects of spasticity, rigidity or paralysis. The facial expression in laughter waxes and wanes slowly. A sudden explosion of laughter may persist

like a sustained clonus, and the noise made may be prolonged and distorted to a scream or a wail. The sound and appearance resembles that of a laughing or weeping infant. Sialorrhœa and dysphagia with choking are common, and the jaw-jerk is increased. Disorder of conjugate ocular movement on upward, downward or on lateral gaze, or bilateral lid retraction may accompany these phenomena. Evidences of bilateral pyramidal disease are usually, but not invariably, present. This condition is known to all of you and I propose to describe only one arteriosclerotic case.

Bulbar symptoms may result from symmetrical cortical lesions as in the following case (Friedman, 1939):

> Autopsy showed almost symmetrical softenings of the lower portions of both motor areas low down.
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> "The patient presented signs of almost complete bulbar paralysis. The tongue lay limp in the floor of the mouth. She was unable to swallow or to show her teeth. She was, however, subject to sudden outbursts of uncontrolled laughter, so that the ward was in a constant uproar. During these spells emotional or mimetic movements of the facial muscles functioned excessively.
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> "This case demonstrated in almost experimental fashion the dissociation between *voluntary* innervation of the facial muscles and the *involuntary* innervation, which is supplied by way of the so-called facio-respiratory pathway. The voluntary pathway was seemingly damaged on both sides and therefore released the involuntary pathways with resulting gales of laughter."

In pseudo-bulbar cases softenings are found in the corpus striatum, brain-stem and pons. Lesions in the cortex are rare (Hughes, Dodgson and Maclennan, 1954). In cases with dementia brain shrinkage may be present.

There are few instances recorded with autopsy findings where pathological hilarity followed a single ictus. The lesion in these cases seems to be a partial occlusion of the vertebral or basilar arteries, producing areas of softening in the mid-line structures of the upper pons or crura cerebri. Thus in C. K. Mills' Case 2 (1912) the lesion involved the red nucleus on the right side and extended across the mid-line to the left crus.

I have not been able to convince myself that pathological laughter has any close association with thalamic hemiplegia. In Wilson's (1924) Case 5 there was no autopsy and the lesions may well have been multiple, and in Weisenburg and Guilfoyle's (1910) tumour case the autopsy showed distortion of the hypothalamus.

Since it has been denied that pathological laughter occurs in bulbar disease, I considered that the study of *motor neurone disease* might be of importance. We know that the lesions are confined to the motor nuclei and tracts.

I studied the case histories of 20 cases of uncomplicated bulbar palsy due to motor neurone disease, discarding all cases with hypertension, gross memory defects or dementia, and those with reactive depression.

The difficulties of distinguishing between the crude bulbar automatisms of mirthless laughter and emotional lability is seen in this group of cases.

Of 12 cases with *extensor* responses (2 unilateral only), 5 cases had disorders of emotional expression described as "poor emotional control," "uncontrollable laughter," "inappropriate laughter," "incongruity of affect (grinned when scolding the children)," "emotional weeping." The others showed normal responses. Of 8 cases with *flexor* responses, 3 had disorders of emotional expression described as "explosive laughter," "emotionally labile (2)." One had an attack of laughing and screaming lasting three hours although not a hysterical personality. The others showed normal emotional responses. One has to explain why in the cases with bilateral extensor responses, 7 had no abnormal emotional display. Presumably sufficient cortico-bulbar fibres remained to exert control over the facio-respiratory nuclei. Three of the cases with no clinical evidences of pyramidal disease had disorders of laughter. The discharge of laughter is in terms of movements, not muscles. The degeneration of bulbar nuclei seems to cause disorder of suprasegmental mechanisms.

Case 1.—*Atrophic bulbar palsy due to uncomplicated motor neurone disease with bouts of laughing or weeping in the early stages of the illness. Plantars flexor right and left.*

W. S., aged 47 *years*, had for eight months complained of inability to formulate words, a sensation of a lump in the throat, difficulty in swallowing, with twitchings in the arm muscles. Normally she was a stable person emotionally, but in the early months of her illness she had irresistible outbursts of weeping or laughter.

On examination, she was not particularly depressed, memory and concentration were good and her mental state appeared normal. The fundi, pupils and external ocular movements were normal. *The jaw-jerk was very brisk*. There was slight weakness of the orbiculares oculi muscles, the palate moved poorly. the tongue was wasted and showed marked fasciculation. The upper limbs showed a loss of power in the right triceps and slight weakness of both wrists and small muscles of the hands. The forearm and hand muscles were wasted and there was occasional fasciculation in the muscles of the shoulder girdles, arms, forearms and dorsal interossei. The tonus was flaccid. The trunk and lower limbs, however, were unaffected. The tendon reflexes showed diminution of the triceps-jerks on the two sides and possibly the ankle-jerks. The abdominals were brisk and the plantars flexor. No sensory changes were present. The blood pressure measured 130/75. The spinal fluid showed less than 1 cell per c.mm. and 20 mg. protein: a negative Lange curve and W.R. X-rays of the chest and cervical spine showed no abnormality. *At autopsy*, the bulbar nuclei were degenerated. No evidence of pyramidal disease was found.

It is suggested that in this case the nuclear degeneration may have produced a secondary effect upon intact suprasegmental mechanisms.

Of 48 cases of bulbar palsy due to motor neurone disease examined by Ragner Müller (1952), 16 had outbursts of laughter or weeping. Only 3 were without clinical signs of bilateral pyramidal disease. No patient in his series had signs of psychological disorder.

It seems that although disorders of laughter are common in pseudo-bulbar cases with bilateral lesions in the hemispheres, they may occur

when the lesions are confined to the bulb. I have observed a case of uncontrollable laughter spells in a case of chordoma attached to the posterior clivus which at autopsy was found to have compressed the pons and medulla chiefly, and to a lesser extent the crura cerebri. A slight degree of hydrocephalus was present in this case.

I find a difficulty in describing abnormalities of laughter apart from the accompanying emotional feeling, for the disintegration produced by disease may cause alteration, not only in the expression of feeling, but in the feeling itself. Patients will say "I cannot keep a straight face. However much I try, I cannot stop giggling. If I didn't laugh, I should cry." Spasms of giggling or loud laughter are often brought on by attempts to talk, by excitement or emotion of any kind. The attempt to conceal these gusts of inappropriate laughter which cause patients social embarrassment, keeps them in a state of continual tension. They bury their faces in their hands in an effort to hide it, they are distressed, not amused. The following patient illustrated this. The clinical picture resembled that of pseudo-bulbar palsy due to arteriosclerosis, but the lesion was a tumour.

Case 2.—*Uncontrollable chuckling on attempting to talk with euphoria in a patient showing bulbar speech, dyphasia, right homonymous hemianopia and right-sided extensor plantar response. Mild confusion.*

T. M., aged 44, a right-handed man, had complained of headaches for nine months. His speech became slurred, he began to talk in short phrases and to chuckle uncontrollably when he tried to talk. He stated that he was unable to control this chuckling. He seemed exaggeratedly happy, showing no evidences of anxiety or mental distress, although he suffered from severe headaches and was prone to almost daily falling attacks in which he fell limply to the ground without apparent loss of consciousness, incontinence or tongue-biting. At times both legs would jerk uncontrollably. All this was in the early stages of his illness.

On examination.—He was euphoric and talked with difficulty owing to dysphasia, slurring dysarthria and uncontrollable chuckling. He was mildly confused and elated. There was blurring of the medial margin of the left optic disc. The fields of vision showed a complete right homonymous hemianopia to the mid-line. The jaw-jerk was increased. An upper motor neurone type of facial weakness existed on the right side and the right plantar response was of the extensor type. The abdominal reflexes were brisk, upper and lower, and there were no abnormal motor or sensory signs. The blood pressure measured 115/80. X-rays of the skull showed marked pressure atrophy of the sella. He became restless and excited and then stuporose, and a week after admission to hospital died, in spite of tapping of the lateral ventricles.

This patient showed exaggerated laughter precipitated by attempts at talking, with dysphasia, euphoria and mild confusion. His disorder of laughter was therefore complex; involuntary laughter was accompanied by disturbances of emotional feeling. Speech disorder and intellectual insufficiency were also present.

At autopsy a glioblastoma occupied the hypothalamus, reaching the surface at the tuber cinereum which it displaced downwards. In the left hemisphere there was tumour-

spread from the mid-line to involve the thalamus, globus pallidus, and part of the putamen, reaching up as far as the caudate nucleus and impinging on the lateral ventricle, into which there had been bleeding. There was a discrete and apparently unrelated area of softening in the subcortical white matter of the left anterior frontal pole, the size of a sixpenny piece. No dilatation of the lateral ventricles existed.

In pseudo-bulbar cases the pathological emotionalism does not necessarily persist. If the patient improves and regains volitional control, the emotionalism lessens or disappears. Curiously it may disappear after a further ictus.

(2) *Fits of Laughter as an Epileptic Phenomenon*

It has long been known (Trousseau, 1873) that bursts of laughter or giggling may constitute an epileptic fit or its aura. The patient is usually, but not invariably, unaware that he has laughed when the attack is over. In Féré's (1898) case, attacks were preceded by loquacity and laughter. In Frigerio's (1899) patient, the laughter was intermingled with babbling speech. Wilder's (1931) case saw fortification spectra and experienced an odour of burning in the attacks, and in the cases of Mills (1912) and Rogal (1937) automatism occurred. The close resemblance of these cases to so-called uncinate or temporal lobe epilepsy is most striking. Incidentally one may remark how these attacks are sometimes attributed to rudeness, hysteria, compulsions of an obsessional kind, early schizophrenia or migraine.

Case 3.—*Psychomotor attacks with "déjà vu" feelings and outbursts of laughter, probably epileptic, in a young man aged* 18 *years.*

C. H., aged 18 *years*, who is left-handed, has complained of strange feelings for two years. In the attacks he has a sense of familiarity with situations—"As if it has all happened before. Something passes across my mind which has been there before. It is like trying to remember a dream. I can remember what I was thinking and doing in previous attacks, but the memory goes as soon as I recover."

He thinks that his attacks are sometimes brought on when he is near bright or flickering lights, and he described one attack in a cinema. He says he does not realize that he has laughed or has had one of his attacks until some hours afterwards, when he manages to remember it. During the attacks he is unable to talk to people.

In addition to these attacks he describes sensory symptoms in which he has teichopsia with spreading numbness in the gums and teeth, the arm and leg, usually, but not always, on the left side. His attacks come about once a week. In one he said he felt cold in the stomach, laughed slightly and felt weak and dazed. Occasionally he has to hold on to things to prevent falling. He thinks that some of his attacks are brought on by being in an embarrassing situation, or when he sees somebody being made a fool of. He does not seem to lose consciousness completely, but has a feeling of recurrence of thoughts that he has had before.

Neurological examination showed no abnormality. Straight X-rays of the head were normal. Several EEG examinations were made, all of them suggesting the diagnosis of idiopathic epilepsy. In one of these examinations a focus was present in the right temporal region, probably not structural.

His attacks are not much influenced by anti-convulsants.

Case 4.—Explosive laughter and giggling as an epileptic manifestation in a child aged 8 years.

Patricia M., aged 8 years, was recently in the Maida Vale Hospital under the care of Sir Russell Brain. Soon after birth she had begun to have two to twelve attacks of laughter during the day mostly, but also in sleep. The attacks came on explosively and suddenly; she either giggled or laughed heartily and then appeared vacant or distressed. Her hands would clench, her arms would shake and her elbows flex. The right corner of her mouth would draw up and in some of the attacks she would be incontinent of urine or would drop things.

The EEG was abnormal and showed a generalized dysrhythmia without any special focus in the temporal lobe. She had no focal neurological signs. After she was put on anti-convulsants she began to have fewer and less marked attacks.

Roubiçek has described personal cases and reviewed the literature (1946).

C. K. Mills (1912) described the case of a young man aged 29 years who had suffered from episodic seizures in infancy. At the age of 19 years he began to have attacks of smiling with disturbance of consciousness and twitchings of the left side of the face. At the age of 25 years he had Jacksonian attacks affecting chiefly the left face and upper limb preceded by a *high-pitched cackling laugh*, then vacancy, then automatic walking. The right frontal lobe was explored by C. H. Frazier and a condition resembling cortical atrophy was found.

I am indebted to Professors Dott and Cappell who allow me to quote the following case, first published by Dott (1938) and referred to by Purdon Martin (1950). The tumour was an astrocytoma of the floor of the third ventricle, whose attachment was restricted to the region of the mammillary bodies. The nuclei of the hypothalamus and the tumour relationships to surrounding structures have now been most meticulously identified by Professor Cappell. This work formed one of the demonstrations at the recent Second International Congress of Neuropathology.

This small girl had fits almost from birth. Delivery had been prolonged, with difficulty in establishing breathing after birth. The character of her fits soon began to change and at the age of 3 her father distinguished *short outbursts of giggling and laughing*, often preceded by an aura of preoccupation. The severe fits were of the *grand mal* type.

During her first years of life she developed signs of precocious puberty—vaginal bleeding, enlargement of the breasts and other secondary sexual characteristics. At the age of 4 she had innumerable *laughing fits* during waking and sleeping hours. In many attacks a *crescendo of laughter terminated in loss of consciousness* with tonic fits.

She was shy and modest for her age. About the age of 4 years she was destructive and malicious. Between 4 and 8 years she spoke little. Throughout her life she showed a strange *disorder of emotion*. She was indifferent to her family and others except a girl neighbour nine years older, to whom she was passionately attached in a jealous and possessive fashion. Apart from this, her lack of emotional expression amounted almost to emotional paralysis. Precocious puberty, emotional disorder with fits and fits of laughter constituted the only signs of central disorder.

The autopsy findings were as follows: the tumour, whose attachment was restricted to the mammillary bodies, was large, 4 × 3·5 × 5·5 cm., and projected into the third ventricle. There were no evidences of increased intracranial pressure or hydrocephalus.

The growth had flattened the pons and cerebral peduncles and elevated the floor of the third ventricle which was not dilated. All the hypothalamic nuclei could be identified microscopically.

The case is important evidence of the hypothalamic origin of such attacks. The literature was fully reviewed by Purdon Martin (1950), who quoted Gerard Lefebvre's (1939) case of probable hypophyseal tumour, and described the autopsy findings in a striking case of his own, who died soon after the onset of fits of laughter from rupture of a saccular basal aneurysm involving the corpora mammillaria. His patient died from subarachnoid hæmorrhage. Purdon Martin considered that the apparent mirth in such cases is "sham" and that the patient's emotional state in such an attack is not that of amusement or joy. The laughter may or may not be remembered, it may be transient or prolonged, occurring during sleep or in the waking state with or without disturbance of consciousness.

The following case, that of a small girl aged 11 years, showed bouts of spasmodic *weeping* culminating in unconsciousness and falling. A basal glioma filled the interpeduncular space and involved the upper part of the pons. The case was published by Purves-Stewart and was once under my care.

Case 5.—Attacks of explosive uncontrollable weeping culminating in unconsciousness in a girl aged 11 years, with chiasmal blindness.

A. B., a small girl, aged 11 years, began to have occasional causeless vomiting. This was followed six weeks before admission by *uncontrollable attacks of weeping culminating in unconsciousness.* In these attacks she fell down with clenched fists, but her knees were said to crumple up under her. Before these attacks she complained of being unable to see clearly and her face was flushed.

She was admitted to hospital as a case of hysteria, but it was clear that she was blind, although the optic discs and fundi were normal. The pupils, widely dilated, were inactive to light, at times the left was larger than the right. The arm-jerks and the knee- and ankle-jerks were absent. The abdominal reflexes were feeble, the left lower abdominal was absent. Both plantars were flexor. Kernig's sign was positive.

Several convulsive attacks occurred before death two to three weeks later. The patient had developed a right oculomotor paralysis and bilateral extensor plantar responses.

At *autopsy* a basal glioma was found in the interpeduncular space infiltrating the upper part of the pons, the third nerve and the optic chiasma. The tumour had extended inwards between the corpora quadrigemina and the iter and both lateral ventricles were dilated.

A relationship undoubtedly exists between natural laughter, alterations in muscle tonus, and states of sleep or stupor. All may be observed in otherwise normal persons as well as in disease of the basal structures of the brain. Féré (1898) reported a case where fits of laughter were followed by an irresistible desire to sleep.

True *narcolepsy* with cataplectic attacks in which emotional disturbance, especially laughter, results in toneless collapse without loss of conscious-

ness, may be due to some diffuse disease or injury to the hypothalamic areas. Laughter of the normal hearty kind may precipitate fits in epileptically predisposed individuals, and people with pathological narcolepsy may develop epilepsy later in life.

I have never myself known true narcolepsy conditioned by normal laughter to be associated with a brain tumour.

In other cases the laughter is prolonged and ends in hemiplegia, a fit, stupor or dementia. This has been called " Ictus ridenti."

Cases of prolonged laughter followed by hemiplegia, stupor or dementia (ictus ridenti) are here considered in the epileptic group. The laughter spell in such cases may last hours, or as long as weeks. Many but not all have cerebral arteriosclerosis. Féré (1903) called this phenomenon "Le fou rire prodromique."

One of Féré's two cases was that of an advocate, aged 64 years, a grave, serious and reserved person. He began having bursts of uncontrollable laughter, the more severe ones being followed by an irresistible desire for sleep. Four months later, consequent upon a laughter spell, he developed a left hemiplegia and survived for eighteen months after the attack, somewhat demented. The hemiplegia put an end to his attacks of laughter. This is not always so. A subsequent ictus may cause recurrence of bouts of laughter after a period during which emotional stability has been regained. In Andersen's case (1936) the autopsy showed that intracerebral and ventricular hæmorrhage from a penetrating branch of the posterior cerebral artery caused death. After sudden epileptic laughter with upward deviation of the eyes which lasted for an hour and a half, the patient, a known pseudo-bulbar case, developed not hemiplegia but coma and died in twenty-four hours. Post-mortem examination of the brain showed softenings in both hemispheres. Recent intracerebral hæmorrhage had destroyed both internal capsules and filled the third ventricle. Both thalami were partly involved in the destruction. The blood filling the third ventricle had spread down the iter into the fourth. There was no subarachnoid hæmorrhage. Badt's (1927) case showed bilateral thalamic hæmorrhage.

In the case of Meige and Béhague (1919) the patient had had craniotomy for a large traumatic subdural hæmatoma following head injury due to shrapnel. There had been dural penetration. Long spells of laughter (one lasted fifteen days) eventually gave way to attacks of laughter with loss of consciousness and convulsions.

The long duration of the laughter in these cases seems to be related to active destruction of brain tissue by a gradually increasing hæmorrhage.

The following personal case illustrates "Le fou rire prodromique."

Case 6.—*Mrs. E. C., aged* 58, had five years previously had a stroke, after which she dragged the right foot. Two years later she had another more severe stroke which

affected the left side, and after this she lived only a bathchair existence, although she could walk with little steps unaided.

One evening she had a sudden giddy attack, in which she fell to the floor. She managed to get into her bed without help. She then commenced to laugh and continued to laugh continuously for three hours, becoming more and more exhausted. At the end of this period she passed into a stupor lasting eighteen hours. After she regained consciousness she was found to have a severe right hemiplegia with dysphasia and she was doubly incontinent with mild dementia and bilateral extensor plantar responses. During the last three years of her life, following upon this attack, she used to laugh immoderately at trivial causes.

(3) *Disorders of Laughter Consequent upon Excitement, Euphoria and Other Mental Changes*

States of excitement (or apathy) due to discrete brain lesions may cause laughter, hilariousness, and an excessive feeling of well-being. Such symptoms have long been known to follow lesions of the orbital part of the frontal lobe. Diffuse cerebral intoxications or anoxia as well as psychotic states cause similar symptoms. Many of the recorded cases are tumours involving the hypothalamus or its connexions.

One of the earliest cases recorded is that of Bruce (1883), where a patient with a temporal lobe tumour suffered from fits of excitement with laughing and crying. His patient became dysphasic.

Van der Horst (1953) described a case of slow-growing glioma of the left temporal lobe which gradually over a period of years destroyed most of the limbic lobe and hypothalamus. This case at one stage had bouts of excitement in which he made speeches in jargon language with violent rhetorical expressive gestures. As the fit came to an end after three minutes his voice would sink to diminuendo and a smile would spread over his face. His recollection of these attacks was imperfect.

Lesions of the third ventricle and hypothalamus as well as cortical lesions may be associated with symptoms resembling psychosis or dementia—particularly states of stupor. This was described by Cairns (1952) in children. Occasionally, however, in hypothalamic lesions episodic *states of excitement* with laughter occur with hilarious or obscene talk, usually as a prelude to stupor with dementia or death. The subject has been fully dealt with by Cox (1937), who described hypothalamic tumours and other basal lesions producing exalted states of consciousness with excitement. The phenomena resemble those of psychomotor epilepsy, but terminate in confusion or dementia. Foerster and Gagel (1933) had noted disturbances of this kind whilst operating upon patients under local anæsthesia. One patient (Case 3), operated upon for a craniopharyngioma, was lying quietly upon the table until piecemeal removal of his tumour was attempted. He then began to talk incessantly, made jokes, witty remarks, gesticulated with his hands and feet and made quotations in Greek, Latin and Hebrew. He gradually became more and more incoherent. After the operation he was demented and confused. Hyperpyrexia occurred and he died.

Two other cases described by them are of interest. In Case 4 (papilloma of the choroid plexus) whilst they were swabbing blood from the third ventricle, the patient became lively and talkative, joking and whistling. This type of response seemed to be obtained by touching the infundibular region. After operation the patient became confused and died with hyperpyrexia. In their Case 5, touching the infundibular region caused the patient to become excited and sing. Schuster (1902) (quoted by Cox) had previously described excitement with diencephalic tumours.

Percival Bailey (1948) described attacks of laughing and weeping with excitement, sleeplessness and pyrexia in a boy aged 13 years during the recovery phase after removal of a third ventricle tumour. The patient regained his emotional control within three weeks and made a satisfactory general recovery.

In Cushing's (1912, "The Pituitary Body and its Disorders") Case 17, a large interpeduncular growth in a man aged 35 years was associated with emotional changes: he was over-hilarious or lachrymose by turns, loquacious and irrelevant, irritable and forgetful, but not disoriented.

At autopsy, the tumour, an infundibular "teratoma" can be seen in the photograph to have elevated the floor of the third ventricle, widening the interpeduncular space, flattening the pons and elongating the mid-brain. The floor of the third ventricle, the mammillary bodies and the pituitary were compressed but intact. There was moderate hydrocephalus.

Deep indentation of the under surfaces of both temporal lobes was observed in this case. It seems likely that this caused damage to cortico-bulbar tracts.

Davison and Kelman's (1939) Case 32, showed at post-mortem a left-sided meningioma lying near the mid-line, invading and destroying the left portion of the hypothalamus, the lateral thalamic nuclei, globus pallidus, subthalamic body, cerebral peduncle and mesencephalon.

He had recurrent spells of stupor with spastic right hemiparesis and right-sided hypalgesia. His appearance was Parkinsonian. The right pupil was larger than the left and there was weakness of elevation and depression of the eyes. Lateral gaze was impaired to both sides with nystagmoid jerks.

Between bouts of stupor he laughed or cried involuntarily, without feelings of sadness or happiness. He was rather lethargic, but not dysphasic. The right plantar response was extensor.

Here emotional expression was dissociated from feeling in his spells of laughing and crying. There was notable destruction of part of the mesencephalon as well as diencephalic invasion. The association of emotional apathy in this case is of interest. The line of distinction between such cases and epileptic discharges is hard to define.

In *euphoria* an excessive feeling of well-being is expressed positively by frequent laughter, not spasmodic, and negatively by the absence of anxiety or mental uneasiness. The condition is less common than was believed in advanced multiple sclerosis. In such cases lesions in both hemispheres are present, involving cortico-hypothalamic tracts. The condition recalls "anosognosia" where the patient will not admit the existence of his hemiplegia or other gross neurological lesion.

In *hyperpathia* found in thalamic hemiplegia with disease of the ventral

postero-lateral nucleus of the thalamus an excessively pleasant emotional quality is imparted to the perception of peripheral sensations.

In the "*Witzelsucht*" of rare cases of frontal tumour, pathological joking and punning exist with emotional blunting and lack of social restraint. Such cases are vastly amused by their own jokes, which do not usually amuse others. Facile laughter consequent upon emotional liability is found in cases with defective memory and attention, or defects in perception of time and space due to gross disease of the cortex or cortico-hypothalamic tracts.

Disorders of Smiling

Paralysis of the emotional and expressive movements of the face occurs without corresponding disturbance of voluntary facial movements when carrying out definite tests at command, such as showing the teeth or whistling. This is referred to as "Hypomimia" or "mimic paralysis." *In such cases there is no disorder of emotional feeling, nor release of the laughter mechanism.*

There are many fallacies associated with the identification of this physical sign. It may occur as a personal peculiarity without known physical lesion. It may be simulated by unilateral Parkinsonism producing rigidity, or by unilateral cerebellar disease producing hypotonia of the facial muscles on one side. The usual explanation is that it is due to involvement of "psycho-bulbar tracts" connected with facial emotional expression.

It is found characteristically in deep centrally placed lesions of the contralateral temporal and frontal lobes. Its mechanism is obscure. We know that in hemiplegia an affected muscle may be paralysed for one function and not for another. The same may be true for the facial muscles which are under both pyramidal and extrapyramidal control. In normal smiling there is innervation of certain muscles and relaxation of others, i.e., there is reciprocal innervation. In temporal or frontal lesions the facial muscles may be paralysed for one function predominantly. The converse may be seen after hemispherectomy, where lower facial weakness of voluntary movement is accompanied by a smile which is free and equal on the two sides.

Some cases of Parkinsonism with paralysis of facial expression complain that they are unable to laugh or to enjoy a joke as they did before the onset of their illness.

Discussion

None of the foregoing observations can be held to refute the commonly accepted view that pathological laughter disorder is most frequent in *disease of both hemispheres* interfering with cortico-hypothalamic and cortico-bulbar tracts (voluntary and involuntary) controlling facio-respiratory mechanisms.

In cases recorded of laughter disorder occurring with single hemiplegia it is exceedingly difficult to exclude the presence of pathological changes in the sound hemisphere. Autopsies on cases are few and poorly documented.

Laughter disorder does not appear until after a second ictus in the sound hemisphere. A further ictus may, in some unexplained way, cause either disappearance of the laughter or its recurrence. The frequency of laughter disorder in the pseudo-bulbar types of cerebral arteriosclerosis may perhaps be related not only to the bilateral distribution of the lesions, but also to their frequent distribution in the basal ganglia. In cases with laughter disturbance who survive, a measure of control is regained and the disability becomes much less evident.

In uncomplicated bulbar palsy due to motor neurone disease laughter disorder may occur. It may be impossible in certain cases to find clinical or pathological evidences of pyramidal disease, although the motor nuclei of the bulb show evidence of damage. Of 8 cases of bulbar palsy with disordered laughter, I found 3 showing no pyramidal signs, and 1 with no pathological evidences of pyramidal disease, although the bulbar nuclei were partially destroyed.

It has been stated that laughter disorders do not result from pathological lesions situated below the hypothalamic or mid-brain level. I have produced evidence that this is a fallacy.

Single lesions, if appropriately placed, also cause pathological laughter. Noteworthy in my cases, as in Purdon Martin's and Davison and Kelman's, is the frequency of mid-line lesions, especially those involving the posterior hypothalamus and mid-brain.

The role of the hypothalamus has not, in my view, received sufficient attention. For the production of an emotional response, whether of laughter or of weeping, some degree of integrity of the hypothalamic nuclei seems to be essential. When these nuclei or the cortico-hypothalamic tracts are destroyed, emotional deadness and apathy are much more in evidence than hilarity and excitement.

Lesions of the posterior hypothalamus seem to cause a pathological laughter which is secondary to excitement of the emotions. When there is also excited manic talk, cortical mechanisms must also be stimulated. Many of the hypothalamic lesions are large and expand laterally. They may be seen to cause a deep guttering of the medial aspects of both temporal lobes. Such indentations may interfere with cortico-bulbar fibres controlling the facio-respiratory mechanisms in the bulb.

The classification as epileptic of more prolonged fits of laughter, followed by hemiplegia or stupor, seems justifiable on the analogy of the Jacksonian attack followed by paralysis, or of the epileptic motor aura followed by unconsciousness. They generally occur during progressive brain destruction by a hæmorrhage.

Temporal lobe attacks with laughter.—The association of laughter with speech disturbance and excitement in rare cases of attacks of epilepsy of the temporal lobe type is of great interest. It is well known that psycho-sensory attacks are often accompanied by inappropriate emotional feelings of well-being, anger, misery, fear, unreality, excitement. Motor accompaniments are observed adapted to such feelings, such as running or violence. Laughter or weeping, excited speech, jargon talk, in such fits may have a similar explanation. The idea is gaining ground that the temporal lobes (possibly the limbic structures especially) are important in the elaboration of emotional feelings and states of emotional experience. It may be recalled that Penfield (1950) observed that electrical stimulation of the temporal lobe in the conscious patient caused the recollection of past experiences of a whole chain of events, with an altered affective tone.

An analysis of these cases suggests that abnormal laughter responses can be produced by lesions at various neurological levels including the bulb. The wide distribution of the lesions is noteworthy.

Theoretical

The increase in our knowledge of the central architecture of the autonomic system is one of the most striking modern advances in anatomy and physiology. In the earliest years of the century the central origin of the cervical sympathetic was represented on anatomical diagrams by a blob in the region of the medulla. Later the hypothalamus (somewhat conservatively described as the "head ganglion" of the autonomic system) was added. Nowadays, following on the work of Ranson (1934) and Le Gros Clark (1938), it is clear that we must superimpose other structures upon our diagrams of the hypothalamus, particularly the limbic structures and certain upward tracts to the orbital cortex, and downward tracts to the reticular formation and the bulb. Some of these tracts activate, others inhibit. Systems of fibre tracts may exist within the brain in a state of balance or equilibrium similar to that which exists between the sympathetic and parasympathetic.

The "limbic" lobe was so called by Broca (1878) because it forms the medial "limbus" or limit of the general cavity of the hemisphere. One of the earliest comparative anatomists to link the hypothalamus with the limbic structures was G. Elliot Smith (1919). He suggested that the cortex, which is developed in association with the olfactory apparatus and the hypothalamus, provides a system for integrating an animal's various sensory impressions and imparting to them the quality of emotion. Many neurologists on the basis of study of lesions of the temporal lobe and temporal lobe epilepsy hold the view that structures in the temporal lobe are important in the development of emotional feelings and experiences.

Downward tracts from the hypothalamus, medullated and non-meduliated, appear to end in the reticular formation of the bulb. They may be important in regulation of respiration and other autonomic activities. It is suggested that facio-bulbar automatisms of laughter are mediated by such tracts and that they are the "final common pathway" for laughter.

Schaltenbrand and Girndt (1925) and Bard (1934) have shown that "sham rage" in animals can be demonstrated in various diencephalic preparations. In mid-brain decerebrate preparations the typical reaction is said to be more modified, partial and transient. The placid activity of such a prepared animal belies its ferocious appearance. These reactions have been called "pseudo-affective." In these preparations emotional feeling was judged by the animal's behaviour to be absent or disproportionate to its appearance. It was on this analogy that Purdon Martin termed attacks of mirthless laughter in disease states, "sham laughter," an apt comparison.

What experimental physiologists have produced from diencephalic stimulation is in some ways similar to what is seen in disease, i.e. positive or negative fragments of a total response. By stimulation or by destruction they have produced grimaces, respiratory arrhythmia, phonation; or on the other hand akinetic mutism or poverty of movement.

Neurologists and neurosurgeons have contributed most to our knowledge of laughter and weeping. Neurologists, by their studies of focal lesions and psycho-sensory epilepsy, have shown the relation of laughter, weeping or emotional states to the hypothalamus, the temporal lobes and their connexions. Neurosurgeons have demonstrated that stimulation of the posterior hypothalamus caused excited behaviour with laughter and manic flow of talk.

The mechanistic theory of motor pathways proposed by Wilson is a most useful practical concept, but, as he himself admitted, it is not a complete explanation. Samson Wright (1952) modified it to include the hypothalamus, in his diagram of the efferent pathways for emotional expression. Still, in my view, no complete explanation can be given. I am not proposing to advance the view that the hypothalamus is a laughter centre. Normal laughter has affinities with speech and mental processes. I think the effects of stimulation or destruction of hypothalamic structures are more likely to be due to their connexions with other parts of the brain. Euphoria and smiling may have to do with upward discharges from the hypothalamus, and the low-level dissociated bulbar and respiratory automatisms of laughter with downward discharges from that area.

These responses, however, normally seem to be subordinate to the will and under the domination of both hemispheres. They may be activated reflexly by psychical or peripheral afferent stimuli.

Of natural emotional states, Hughlings Jackson (1931) said: "I believe there is a duplex condition in emotional states, negative (loss of control), and positive (overaction of lower centres)."

In a normal emotional response in man involving laughter, we may say that there is a sensory phase, a mental phase involving psychological processes such as cognition, conation—when we "see a joke" or "have our sense of humour tickled." Finally there is the motor or expressive phase. The new cortex as well as the old cortex of the limbic lobe plays its part in emotional reactions. These manifestations of feeling have affinities with speech and gesture and partake of the neurological complexities of both. There is a language of feeling as well as of thought, but it is at a subordinate level of integration. In this subordination not one but both hemispheres seem to participate.

When we consider abnormal laughter responses we may say that lesions in widespread areas of the brain cause abnormal emotional activity at various levels.

(1) At the lowest level—as at the highest—involuntary, uncontrollable spasms of laughter or weeping occur which do not conform in degree or duration to emotional feeling and in which an appropriate stimulus may be lacking. They commonly cause embarrassment and distress to the patient. Mental changes and disturbances of consciousness are absent. These occur in patients with lesions of the facio-respiratory bulbar nuclei and suprasegmental motor tracts. The majority but not all show signs of bilateral pyramidal disease.

(2) At the intermediate (posterior diencephalic and limbic level) a convulsion of laughter analogous to Jacksonian epilepsy may occur with or without disturbances of consciousness. Laughter may constitute the prodrome of an attack or the attack itself. These attacks often resemble temporal lobe fits. Sudden hypotonia may induce falling.

(3) At the highest level (anterior hypothalamic, frontal, temporal) emotional lability or emotional incontinence is part of a complex mental disorder shown by excited speech or behaviour and giggling. Some mental functions may be stimulated, others paralysed. Here there may be coexistent deficits of memory, attention and perception. Large lesions situated near the mid-line cause disturbances at this level. There may be associated dysphasia, dyspraxia, hemiplegia or visual field defects.

These levels, however, are not clearly defined clinically. In cerebral localization it is not the emotional disorder, but rather the associated somatic findings which indicate the site of the lesion.

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A NEW CONGENITAL NON-PROGRESSIVE MYOPATHY

BY

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DISEASES of skeletal muscle occurring on or about the natal period have been traditionally separated into two groups. The largest group is comprised of infants with weakness and hypotonia (floppy infants). The second and smaller group are those infants with myotonia and no demonstrable weakness (Thomsen's disease or myotonia congenita).

We are concerned in this study only with the first group. There are many causes of hypotonia and muscle weakness in infancy. Among these are mental retardation, rickets, cretinism, myasthenia gravis, achondroplasia and infantile scurvy. After elimination of these disorders, three primary groups remain: (1) progressive spinal atrophies of infancy (Werdnig-Hoffman's disease); (2) progressive muscular dystrophy occurring early in infancy. Both of these disorders, according to classical descriptions, are progressive; (3) a symptom-complex reported by Oppenheim (1900) in which he described infants who were characteristically flaccid from the time of birth and whose extremities could be placed in bizarre postures. There was profound weakness, more in the extremities than the trunk. The lower extremities were most severely involved. The deep tendon reflexes were decreased or absent. He further noted that certain power of movement was retained, particularly with effects of gravity eliminated. Such cases were capable of gradual improvement. Oppenheim believed that the disease began before birth because many of the mothers noted reduced fœtal movements during gestation.

Unfortunately, no biopsy or necropsy material was obtained from the patients described by Oppenheim. It is conceivable, therefore, that more than one disease was present in the syndrome.

As biopsy and necropsy material have subsequently become available on hypotonic infants, opinions have changed as to whether a true infantile myopathy may exist. A brief historical review of the conflicting opinions is pertinent at this time.

Hypotonic infants were first described by Hoffmann (1893). He listed the symptoms as follows: The cases were usually familial. The onset occurred in a previously healthy infant during the first year of life. There

was a gradual increase of symptoms. Proximal muscles were more involved than distal. Eventually bulbar and intercostal muscles were affected leading to death, usually within two years. Pathologic material was available to Hoffmann and he verified that this was a disease of the anterior horn cells and ventral roots.

In 1900 Oppenheim described the symptom-complex discussed above. Batten later (1903) presented three cases of "infantile myopathy" to the Royal Society of Medicine. No histologic studies were available. However, Spiller (1905) presented the necropsy findings of a hypotonic infant thought by him to be an example of Oppenheim's disease. The tissues examined showed no change within the central nervous system. The striated muscle fibres were universally small.

Collier and Wilson (1908) published their review on the subject of amyotonia congenita three years after Spiller's case. They came to the conclusion that the syndrome described by Oppenheim was valid and that this represented a new disease. They listed seven criteria which in their opinion established the diagnosis: (1) There was no familial tendency in amyotonia; (2) no case of amyotonia had been reported in a myopathic family; (3) a large majority of cases of amyotonia were congenital; (4) the characteristic flaccidity of amyotonia was not present in myopathy; (5) local wasting was not present in amyotonia; (6) the course of myopathy was progressive, whereas the course of amyotonia was progressive amelioration; (7) the deep tendon reflexes returned. Again no biopsy or necropsy material was presented.

Reuben (1917) reviewed 136 cases from the literature of what he termed amyotonia congenita. In the majority of the cases which came to necropsy, disease was found in the anterior horn cells or ventral roots. Reuben added no biopsy or necropsy material of his own.

Greenfield and Stern (1927) on the basis of the literature and of a family examined by them with detailed post-mortem and biopsy material came to the conclusion that the disease described by Werdnig and Hoffmann and the syndrome described by Oppenheim were actually one and the same. They further emphasized that the criteria for diagnosis outlined by Collier and Wilson (1908) were not valid for the following reasons: (1) Sporadic cases of Werdnig-Hoffmann's disease may be seen. (2) Infantile spinal atrophy may be noted on or about birth. (3) Characteristic adipose distribution of infancy would mask any local wasting. (4) Spontaneous periods of remission up to two years could occur in infantile spinal atrophy.

The majority of investigators agreed with Greenfield and Stern. An exception was noted, however, in the cases reported by Turner (1940). Turner had the good fortune of examining the family originally presented by Batten (1909–1910) as infantile myopathy. The pathology in these cases was reviewed by Greenfield and he and Turner came to the con-

clusion that these patients at that time represented a *non-progressive myopathy*. A further necropsy of the same family was presented by Turner (1949).

In Turner's last article, a review of the case report, F. S., revealed a definite progression of wasting of the muscles of the shoulder and upper extremity between her admission in 1931 at the age of 11 and in 1938.

From a review of the literature we therefore can find no *pathological* documentation of a non-progressive neuropathy or myopathy, although many clinical cases of hypotonic infants who improve have been reported. Muscle biopsies should be performed on these patients who are not uncommon. We have examined and performed muscle biopsies in three such cases. The picture in the muscle was not unlike that described by Spiller (1904–1905), in that universally small fibres were universally present. As these were sporadic cases, only time will determine the ultimate outcome in such patients. Since the average physician is not in contact with patients for a prolonged period, the only ways of showing non-progression are the examination of multiple generations in a heredo-familial disease, and reliance upon the patient's history. This report, therefore, concerns 5 patients in three generations of the same family with a *non-progressive myopathy* who have a characteristic pathognomonic alteration of the muscle fibre.

Clinical Features

This series consisted of four males and one female occurring in three generations of the same family. Ages, at the time of study in 1956, ranged from 2 to 65. It is evident from fig. 1 that the disorder is heredo-familial. The pattern of inheritance suggests a Mendelian dominant without sex linkage but the number of affected members is not sufficient to state the precise genetic transmission.

The disease was present at birth or shortly thereafter. A history of reduced fœtal movements was obtained in one case. The earliest manifestation of the disease was delayed motor development and bizarre postures (fig. 2). The early history of the older patients is not complete, with the exception that all were delayed in walking until the age of 4 or 5. One of the two children could not turn in bed until 10 months. Once the patients were able to walk, their symptoms, though varying in severity from one to another, were similar. All complained of difficulty in climbing stairs, running, rising from supine or sitting positions, in other words, those activities involving the use of proximal muscles in the lower extremities. The adults gave a history of minimal weakness in the upper extremities, manifest only during vigorous activity involving proximal muscles such as throwing an object or attempting to perform gymnastics. The patients had no *symptoms* suggesting sensory or cranial nerve abnormality. Although probably not related to the disease, asthmatic attacks had occurred in several affected and unaffected members of the

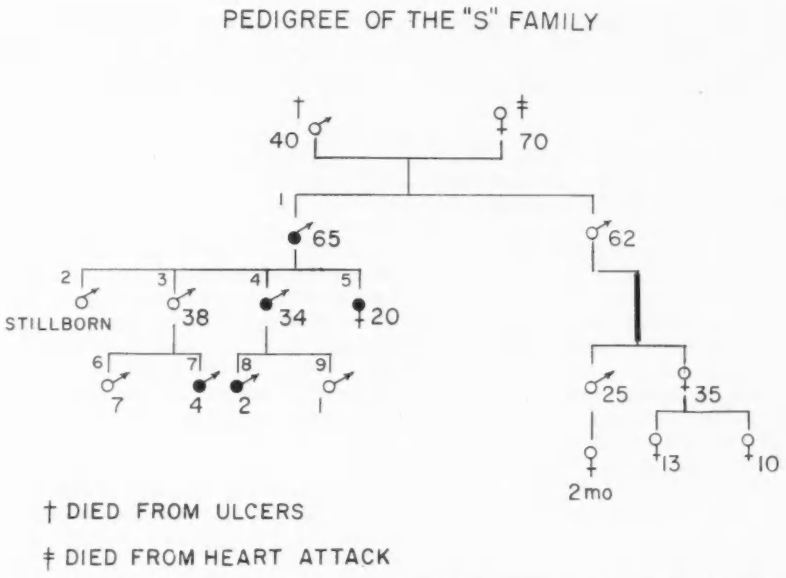

FIG. 1.—Genetic chart of S. family. Affected members are indicated in black. The numbers above the symbols refer to the case numbers in the text. The numbers below the symbols indicate the patient's age.

family. Two affected male members had bilateral inguinal hernias, and the one affected female had an umbilical hernia.

Examination disclosed certain abnormalities present in all affected patients. Muscle weakness was primarily proximal and most severe in the lower extremities. In some of the patients slight weakness was evident distally as well. Despite the weakness, all muscles could be moved against both resistance and gravity. All patients were ambulatory and were able to perform useful occupations. Hypotonia was evident only in the children. Wasting was not a prominent feature, though one patient (Case 4) showed generally poor musculoskeletal development (fig. 2, Plate XLIV). No distinct focal atrophy or fasciculations were observed. In all patients the deep tendon reflexes were normally active and symmetrical. No myotonia could be elicited clinically or electronically. The cranial nerves were normal with the exception of weakness in the sternocleidomastoid muscles and the orbicularis oculi in one patient (Case 4). No sensory abnormalities were detected. Loss of the metatarsal arch was noted in most affected members.

Laboratory studies were normal with the exception of an increase in urinary creatine and a decrease in urinary creatinine excretion. Additional studies directed toward determining endocrine function revealed no abnormality. Electrocardiograms were normal. Roentgenographic

studies were normal with the exception of frequent kyphoscoliosis in two of the adults and bony demineralization in one patient (Case 4). This was of mild degree and its significance could not be determined.

Case Reports

Case 1.—R. S., Sr. (fig. 4), is a 65-year-old white male accountant. The details that surround his birth are unknown except that a breech delivery was performed during a slow birth. He recalls that he did not walk until the age of 4 and that he could not run as fast as other children and had difficulty climbing stairs. To the present time, 61 years later, the patient has noted no significant change in his condition. He is able to walk without difficulty and continues to note weakness only when climbing, rising from a sitting position, or running. He has noted no weakness of muscles innervated by the cranial nerves nor in the muscles of the upper extremity during routine use. With strenuous exercise, as in gymnastics, there is slight weakness of the proximal muscles of the upper extremities.

The patient has had mild asthma and for at least twenty years has had mild hypertension. Otherwise his general health has been good. A right inguinal herniorrhaphy was performed in 1916 and for the past two years he has had a left inguinal hernia.

Examination.—The patient is well developed and well nourished. The general physical examination was within normal limits except for a blood pressure ranging from 190/110 to 140/80 on repeated examinations and an easily reducible left inguinal hernia.

The patient is of superior intelligence. No abnormality was detected in testing of cranial nerves or sensation. In the upper extremities muscle strength was within normal limits to the usual tests of power. The patient's gait was normal but when rising from a lying position, he could not sit or stand without support or without placing his hands on his knees. Specific testing disclosed weakness in the iliopsoas and quadriceps muscles, though movement could still be performed against gravity and mild resistance. The other muscles in the lower extremities were of nearly normal strength. Muscle bulk was normal. No fasciculations or myotonic reaction could be elicited. The deep tendon reflexes were normally active and equal. There were no pathological reflexes or involuntary movements.

Laboratory studies.—Blood count and urine were normal. Blood serology was negative. Blood studies disclosed: blood urea nitrogen, 17 mg./100 c.c.; creatinine 0·6 mg./100 c.c.; glucose, 103 mg./100 c.c.; calcium, 10 mg./100 c.c.; inorganic phosphorus, 3·5 mg./100 c.c.; alkaline phosphatase, 1·6 Bodansky units; total protein 6·3 gramme/100 c.c. with 3·2 albumin and 3·1 globulin. Twenty-four-hour urinary excretion of creatine was 848 mg. and creatinine 697 mg. Basal metabolism was +29·1 per cent (Aub-Dubois) and a radioiodine uptake study at the end of twenty-four hours was 21 per cent, within the range of normal. An electrocardiogram was normal. Roentgenograms of the skull, spine, and chest were within normal limits for the patient's age. No evidence of spontaneous electrical activity or after-discharge following passive or active stimulation could be found in the electromyogram.

Case 2.—A male, stillborn, the first child of Case 1 would have been 40 if alive.

Case 3.—R. S., Jr., a 38-year-old white male naval officer has been in good health throughout his life without any serious illness, except for occasional asthmatic attacks. He was personally examined and a complete neurological examination disclosed no abnormality. In particular, muscle strength was excellent.

Case 4.—B. S., Sr. (fig. 3), is a 34-year-old white male electronic technician. He was the product of a normal gestation. His delivery was breech but uncomplicated. During the first year of life weakness of the legs was noted. Mental development was normal. The patient remained weak, and was unable to stand or walk until the age of 5. At that time, physiotherapy was given, and by the age of 6 he was able to walk without support. Slight improvement continued to the age of 8, but his course then became stationary, and has not changed to the present time. During early childhood a kyphoscoliosis had slowly developed. The weakness has never been accompanied by sensory disturbance or complaints referable to the bulbar musculature. The main difficulty through the years has been in running, climbing, and rising from a supine position. Weakness in the upper extremities is noted only when doing vigorous exercise utilizing proximal muscles as in attempting to lift himself with his hands or throwing an object. He has always been small, with his weight averaging about 90 lb. and he ceased growing in height at the age of 14. Intermittent asthmatic attacks have occurred since childhood. A bilateral inguinal herniorrhaphy was performed at the age of 18.

Examination.—The patient was 60 inches high and weighed 90 lb. The general physical examination was within normal limits with the exception of a thoracic kyphoscoliosis with the convexity to the right and "flat feet." The patient was of superior intelligence. Cranial nerve examination disclosed weakness of the orbicularis oculi and sternocleidomastoid muscles, although movement could still be performed against resistance. Sensory perception was normal. A waddling lordotic gait was evident. When trying to stand, he had to place his hands on his knees to raise himself. He could not step on a 9 in. stool without support. He was unable to sit from a supine position without using his arms. Definite weakness in the shoulder and elbow muscles of the upper extremities was present. Dorsiflexion of the wrist was slightly weak. In the lower extremities, the iliopsoas muscles were weakest. All other thigh movements were weak, although movement could be performed against some resistance. Flexion and extension of the knees were weak, though stronger than hip movements. Ankle movements were of nearly normal strength. Although the patient's general muscle development was very poor, there was no distinct focal atrophy. No fasciculation or myotonic reactions were observed. Co-ordination was normal and there were no involuntary movements. The deep tendon reflexes in the upper and lower extremities were active and equal. There were no pathological reflexes. Abdominal and cremasteric reflexes were normal.

Laboratory studies.—Blood count and urine were normal. Blood serology was negative. Blood chemistry disclosed: urea nitrogen, 15 mg./100 c.c; creatinine, 0·5 mg./100 c.c.; glucose, 62 mg./100 c.c.; total protein, 6·5 grammes/100 c.c.; with 3·8 albumin and 2·7 globulin; total cholesterol, 184 mg./100 c.c.; calcium 10·7 mg./100 c.c; alkaline phosphatase, 1·5 Bodansky units. Spinal fluid examination was performed and clear fluid was obtained under normal pressure. No cells were observed. Studies of the spinal fluid disclosed: serology, negative; total protein, 28 mg./100 c.c.; sugar, 25 mg./100 c.c.; chlorides, 101 meq/L; colloidal gold, 1100000000. Basal metabolism was +15·9 per cent (Aub-Dubois), and a radioactive iodine uptake study was within the range of normal. Twenty-four-hour urinary excretion of creatine and creatinine was 992 mg. and 691 mg. respectively. Roentgenograms of the chest, skull, and spine disclosed bony demineralization throughout the skeletal study and a thoraco-lumbar kyphoscoliosis with the convexity to the right. The electromyogram and electrocardiogram were normal.

Case 5.—E. S. (fig. 5), a 20-year-old white female student was born after normal

gestation, but again presented in the breech position and was delivered after a version. Within a few months after birth, weakness in the lower extremities was observed. The patient was unable to walk until she was 4½ years old. At the age of 5, an operation for an umbilical hernia was performed. Her main complaint to the present time has been difficulty in climbing, running, or rising from a sitting position. There has been no progression since childhood. A mild kyphoscoliosis developed in childhood and has not changed to the present time. She has noted slight difficulty throwing a basketball and lifting herself with her hands but has no other symptoms referable to the upper extremities. There have been no sensory disturbances or complaints regarding the cranial nerve muscles. The patient has received no specific medical treatment other than the physiotherapy in childhood. Aside from her muscle weakness, the patient has been in good health throughout her life.

Examination.—The patient is a well-developed, slightly obese white female college student. The general physical examination was within normal limits except for a thoraco-lumbar kyphoscoliosis with the convexity to the left and "flat feet." Mental status was superior. The cranial nerve examination was normal except for weakness of the sternocleidomastoid muscles bilaterally. Sensory perception was normal. Examination of muscle strength disclosed that no movements were performed with what would be considered normal strength for the patient's age and build though all movements could easily be performed against resistance. Her gait was waddling. The patient rose from the supine position by "climbing up herself" in typical myopathic fashion. She was unable to stand on a 9 in. high foot stool without support or without bracing her hands on her knees to push herself. She was unable to sit from a lying position without using her hands. Muscle strength seemed weaker in abduction and flexion of the shoulder than in other movements of the upper extremities. In the lower extremities, the iliopsoas were the weakest muscles. Other movements of the hip, however, were definitely weak. Flexion and extension of the knee were weak but of better strength than hip movements. The weakness was symmetrical in all areas. The deep tendon reflexes were active and equal. There were no pathological reflexes. Abdominal reflexes were normal.

Laboratory studies.—Blood count and urine were within normal limits. Serology was negative. Blood chemistry disclosed: urea nitrogen, 14 mg./100 c.c.; creatinine, 0·4 mg./100 c.c.; glucose, 80 mg./100 c.c.; total protein, 7·6 grammes/100 c.c. with 4·2 albumin and 3·4 globulin; total cholesterol, 199 mg. per cent; calcium, 11·1 mg. per cent; alkaline phosphatase, 1·5 Bodansky units. Twenty-four-hour urinary excretion of creatine was 164 mg. and creatinine 313 mg. Basal metabolism was +12·2 per cent (Aub-Dubois) and a radioactive iodine uptake was within the range of normal. Roentgenograms of the chest, skull, abdomen, and spine were normal with the exception of a thoraco-lumbar kyphoscoliosis with the convexity to the left and the apex at L3. An electrocardiogram was normal.

Case 6.—R. S. III, the brother of Case 7, is a 7-year-old white male. His birth and development have been completely normal. In particular there has been no suggestion of any muscle weakness. The patient was seen and a complete neurological examination disclosed no abnormality.

Case 7.—S. S. (fig. 2), a 4-year-old white male was born after a normal gestation and labour. His early development was normal. He stood at 9 months, walked at 14 months and was toilet-trained by 2 years. He talked well by the age of 3. However, slight difficulty in running and climbing was noted shortly after he began to walk. He could go up steps one at a time and use support whenever available.

He could not run as well as other children of his age. However, all ordinary movements in walking were performed normally. There was no complaint referable to the upper extremities or cranial nerves. The patient's parents stated that the difficulty was very mild and they might well not have noted it were it not for the family history of muscle weakness. The patient's general health has been excellent.

Examination.—The patient is a well-developed, well-nourished apparently healthy child. The general physical examination was normal except for "flat feet." He was of normal intelligence. The cranial nerve examination disclosed very slight weakness in the sternocleidomastoid muscles bilaterally but otherwise was normal. Sensory perception was normal. Gait was normal but when attempting to arise from a lying position, the patient "climbed up himself" in myopathic fashion, though he was able to do so promptly and with very little support. When attempting to stand on a 9 in. high stool, the patient stated that he could not do so and demanded support. However, on several occasions he was able to perform this test without aid although it did seem difficult for him to do so. It was difficult to evaluate specific muscles, although the weakness seemed to be limited to the pelvic girdle. There was no distal weakness in the lower extremities and the upper extremities were of normal strength. No atrophy, fasciculations or myotonia were observed. Co-ordination was normal. The deep tendon reflexes were active and equal. Abdominal reflexes were present. There were no pathological reflexes.

Laboratory studies.—Blood count and urine were normal. Roentgenograms of the chest, skull, and pelvis were normal except for spina bifida occulta of the fifth lumbar vertebra.

Case 8.—B. S., Jr. (fig. 6), a 2½-year-old white male was born after a normal gestation with the exception of a threatened abortion at three months. The mother noted that the patient kicked much less *in utero* than his apparently normal brother. Labour lasted twenty-seven hours, but delivery was uncomplicated. Retardation in motor development was noted within the first few months of life. The patient was unable to turn over in bed until he was 10 months old. He did not walk until he was 20 months of age, and definite weakness in the lower extremities has persisted to the present. He has particularly severe difficulty in climbing stairs. He cannot run without falling. No abnormality has been noted in the upper extremities. His mother thinks that it may be difficult for him to hold up his head at times. The general medical history disclosed no other serious illnesses.

Examination.—The patient was well developed and well nourished. The general physical examination was within normal limits except for "flat feet." Mental development was normal. The cranial nerve examination was normal except for bilateral weakness of the sternocleidomastoid muscles. No sensory abnormality was evident, though examination was limited due to the patient's age. He walked with a waddling gait, and, when placed supine, had difficulty in rising, and "climbed up himself" in myopathic fashion. With the examiner's arms in the axillæ, the patient was unable to adduct his arms with sufficient strength to allow him to be lifted and his arms slipped through the examiner's. His grip seemed normal. Evaluation of individual muscle strength was unreliable but it was evident that the weakness was primarily proximal, equal, and worse in the lower extremities. Muscle bulk was good. No atrophy, fasciculations or myotonic reaction were observed. Co-ordination was normal. The deep tendon reflexes were active and equal.

Laboratory studies.—Blood count and urine were normal. Twenty-four-hour urinary excretion of creatine was 520 mg. and creatinine 269 mg. Roentgenograms of the chest, skull, and entire spine were normal. Films of the hand showed normal bone age.

Case 9.—A. S., a 1-year-old boy and brother of Case 8, was born after a normal gestation and delivery. His motor development has progressed normally, and he is at present learning to walk. He has always been very active, and crawls about with speed and agility. The patient was examined at this clinic and no definitely abnormal findings were noted.

Pathology

Biopsy specimens of the vastus lateralis were removed under local anæsthesia from the five afflicted members of the family, and orientated on filter paper so that both longitudinal and cross sections could be cut. Each muscle was then placed in three fixatives: 10 per cent formol saline, acidified Zenker's, and Bouin's solutions. Sections from each fixative were routinely stained by the hæmatoxylin, Gomori trichrome, and hæmatoxylin–Van Gieson methods. In addition, periodic acid-Schiff, with and without diastase staining, was done on all tissues. The Lillie allochrome stain was utilized for staining sarcolemma, and the Feulgen stain for desoxyribonucleic acid in the nuclei.

Control biopsies from patients other than this family were processed simultaneously with the above tissues and a portion of the biopsy material was also sent to an adjacent laboratory for further control.

Gross examination.—The tissue removed from all five members appeared normal in colour and consistency and had normal contractile properties.

Histological examination.—(1) *Pattern of lesion:* No large groups of small fibres could be seen. No focal destruction of isolated fibres was observed.

(2) *Fibre size:* The majority of fibres measured approximately 80 micra in diameter. Centrally placed in the large groups of normal-sized fibres could be found, however, large fibres whose size ranged to 240 micra (fig. 7A).

(3) *Fibre structure:* An area which on low power appeared to be almost amorphous could be seen on cross section in the internal portion of almost each fibre (fig. 7B). Examination under high power (× 1700) showed definite fibrillary structure (fig. 10A). Longitudinal sections revealed such fibrils to run almost the entire length of the fibre (fig. 8A). In the enlarged fibres more than one such area could be seen, and in the very large fibres as many as five such areas could be perceived. Phase microscopy and polarization (fig. 8B) revealed these central fibrils to be normally striated. The size of the sarcomere of the abnormal fibrils did not always equal that of the sarcomere of the normal peripheral fibrils. Such sarcomeres may be of the same size or shorter but never longer.

Occasionally aberrant fibrils would turn from the external layer of the fibre and be seen to enter and mix with the fibrils of the central areas (fig. 9A).

The most striking change can be noted in the histochemistry of the fibrils within the abnormal area. With the Gomori trichrome stain the

peripheral fibrils within the fibre stained red, whereas the central fibrils were blue or azurophilic (figs. 10A and B). The central area gave a more positive periodic acid-Schiff reaction than did the peripheral fibrils. This discrepancy remained after exposure to diastase (fig. 9B). Thus, the positive PAS reaction is related to the substance other than or in addition to glycogen. The fibrils in the central areas were also more argentophilic than the peripheral fibrils.

Examination of cross sections showed an area of relative paucity of fibrils between the central area and the more peripheral fibrils. However, no membrane could be found in this area on examination of hæmatoxylin–Van Gieson or Lillie allochrome preparations.

(4) *Muscle nuclei:* Many internal nuclei were present and could occur in chains. This was particularly true in the large fibres. No difference was seen in the nucleoli after desoxyribonucleic acid stains.

(5) *Fat, connective tissue, and peripheral nerves:* There was a moderate increase of both perimysial and endomysial adipose tissue (fig. 7A). There was no increase of collagen or reticulin. The muscular nerves appeared normal and contained a normal amount of myelin.

In summary, the principal histological change was in the anatomical arrangement and histochemical characteristics of aberrant fibrillary bundles found internally in the centre of almost every muscle fibre. A reconstruction of such a muscle fibre may be seen in fig. 11. Frequent large fibres and central nuclei were the other characteristics of the disease and were present in all afflicted members of the family. In Cases 1, 4, 5, and 8, almost every fibre was abnormal. In Case 7, however, only a few such fibres could be found. This case showed the least clinical involvement.

SUMMARY

A new type of non-progressive congenital myopathy is described.

Certain clinical features of the disease may be summarized and are common to all affected members.

The onset is probably congenital or within the first months of life.

Muscle weakness is proximal and most severe in the lower extremities. However, some proximal muscle weakness in the upper extremities is suggested by history or examination in all cases.

This disorder results in delayed walking.

When the patients do learn to walk, their disability remains stationary.

Hypotonia is evident in the children.

The deep tendon reflexes were normal.

Wasting was not a prominent feature.

There were no associated sensory disturbances.

The cranial nerves were normal with the exception of weakness of the sternocleidomastoid muscles and the orbicularis oculi in one patient.

The principal histological change was in the anatomical arrangement

and histochemical characteristics of aberrant fibrillary bundles found internally in the centre of almost every muscle fibre. Frequent large fibres and central nuclei were the other characteristics of the disease.

ACKNOWLEDGMENTS

We are indebted to Dr. Harry Ong, Washington, D.C., for referring this family to the National Institute of Neurological Diseases and Blindness, to Mr. Fred H. Meiller who did all the photomicrographic work, and to Mr. E. Bourne for the preparation of the histologic sections.

We are grateful to Dr. J. G. Greenfield for his advice and encouragement throughout this study, and to Dr. Glenn A. Drager for his assistance with the biopsies and his advice on the silver preparations.

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LEGENDS FOR PLATES

PLATE XLIV

FIG. 2 (*Case* 7).—Note the bizarre posture in the sitting position.

PLATE XLV

FIG. 3 (*Case* 4).—Note kyphoscoliosis, lordosis, and poor muscular development.

FIG. 4 (*Case* 1).—Note almost normal muscle bulk. In spite of this, the patient had marked weakness of girdle muscles of the lower extremity.

PLATE XLVI

FIG. 5 (*Case* 5).—Note lordosis, kyphoscoliosis, and absence of muscle wasting.

FIG. 6 (*Case* 8).—The youngest affected member of the family.

PLATE XLVII

FIG. 7A (*Case* 5).—9172. Hæmatoxylin and eosin. × 22 (Bouin's). A large fibre may be seen in the centre of the upper group fibres. Note the endomysial fat.

FIG. 7B (*Case* 4).—9145. Gomori Tri-chrome. × 270 (Bouin's). Central areas of compact myofibrils with different staining properties may be seen in each muscle fibre. In the large fibre two such areas may be seen.

PLATE XLIV

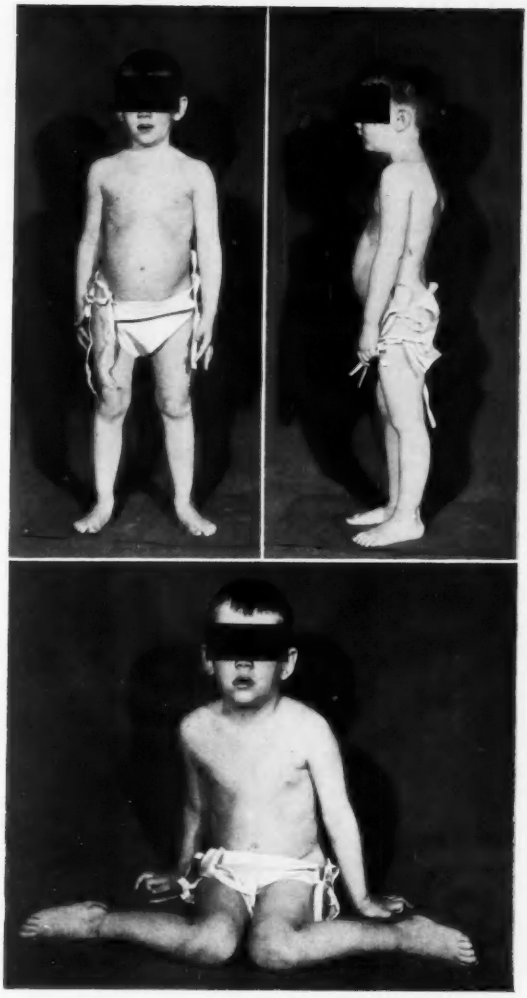

FIG. 2.

To illustrate article by G. Milton Shy and Kenneth R. Magee.

PLATE XLV

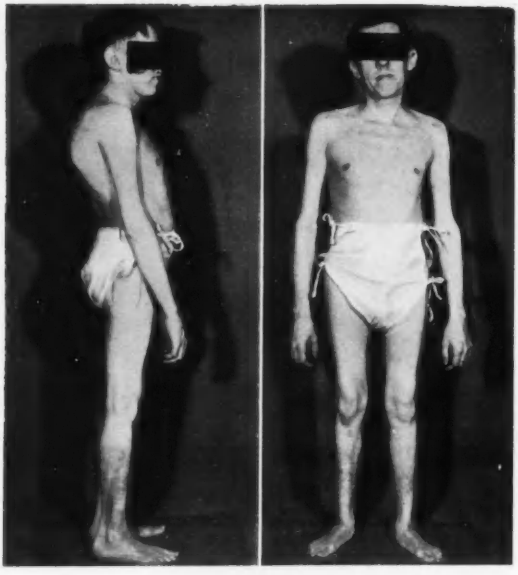

FIG. 3.

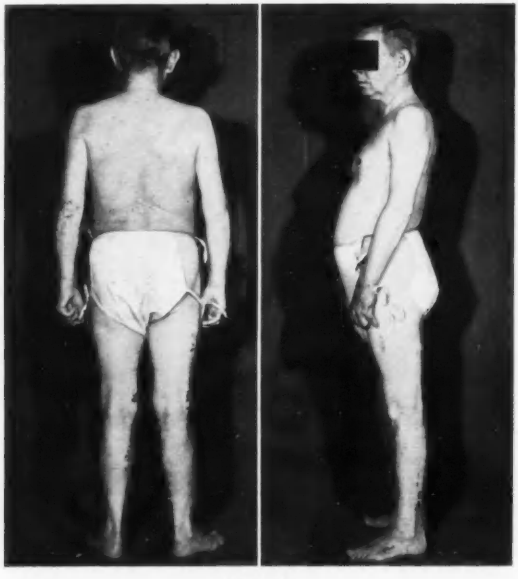

FIG. 4.

To illustrate article by G. Milton Shy and Kenneth R. Magee.

PLATE XLVI

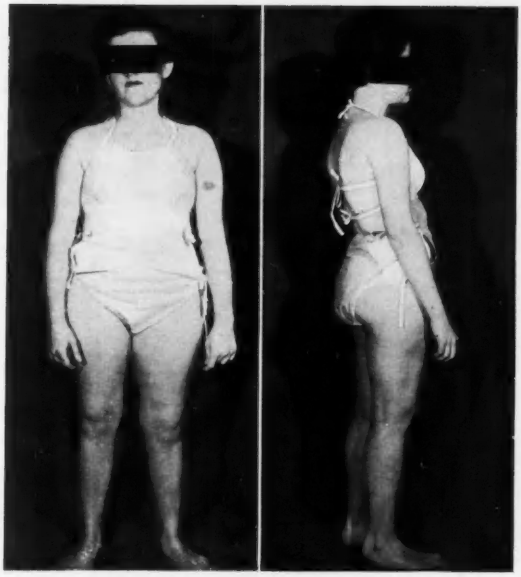

FIG. 5.

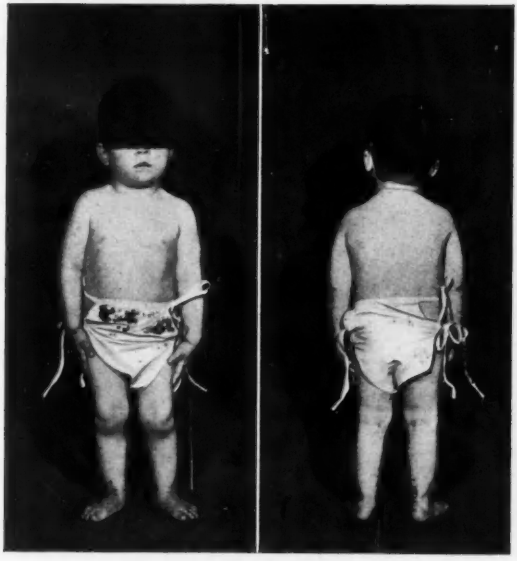

FIG. 6.

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PLATE XLVII

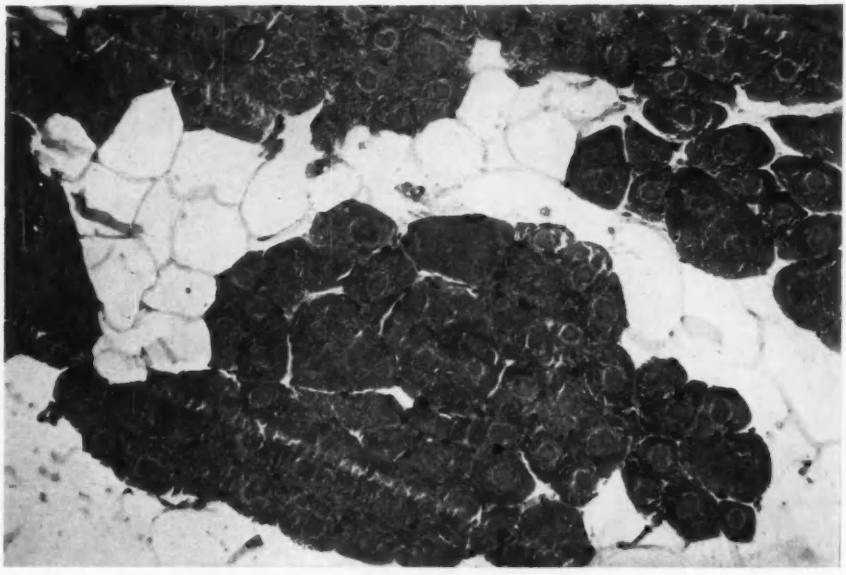

FIG. 7A.

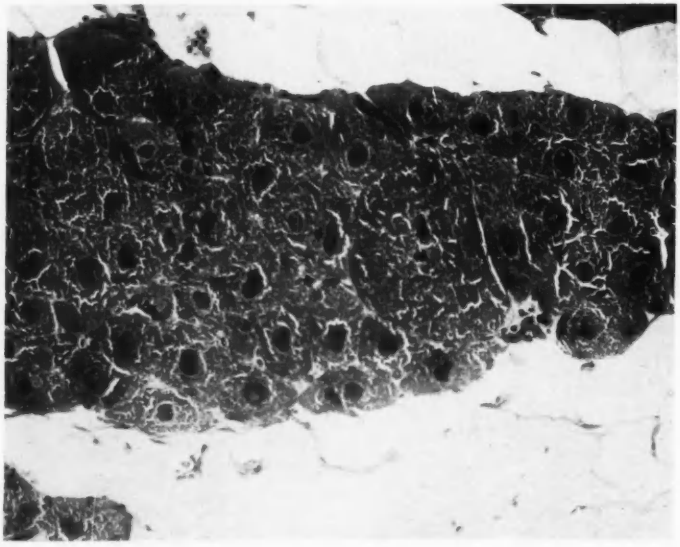

FIG. 7B.

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PLATE XLVIII

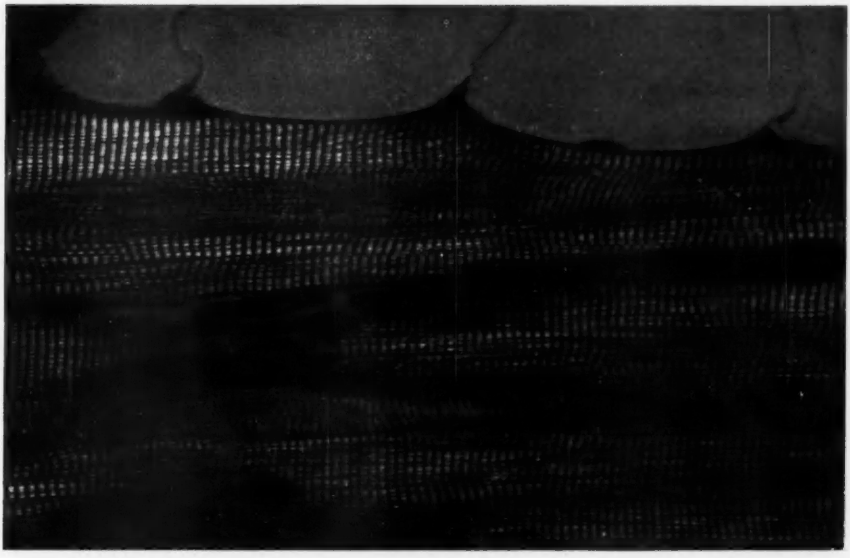

FIG. 8A.

FIG. 8B.

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PLATE XLIX

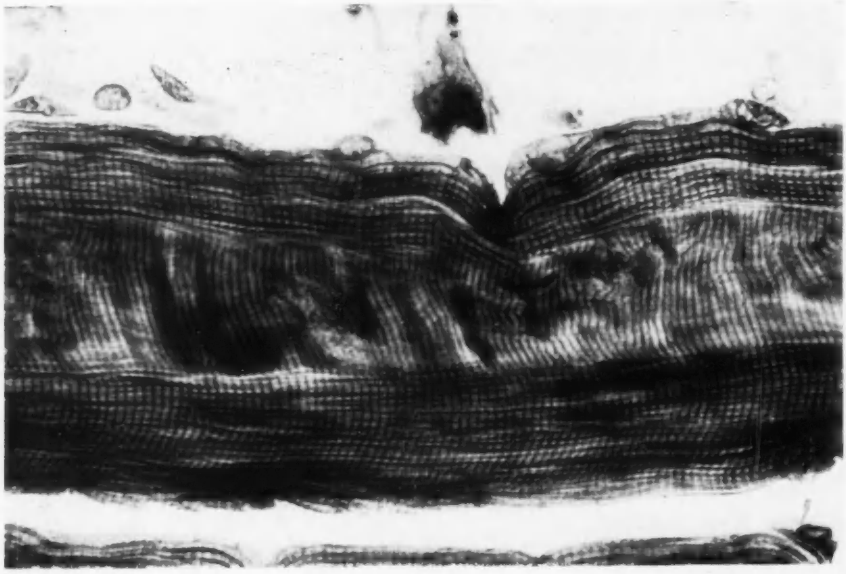

FIG. 9A

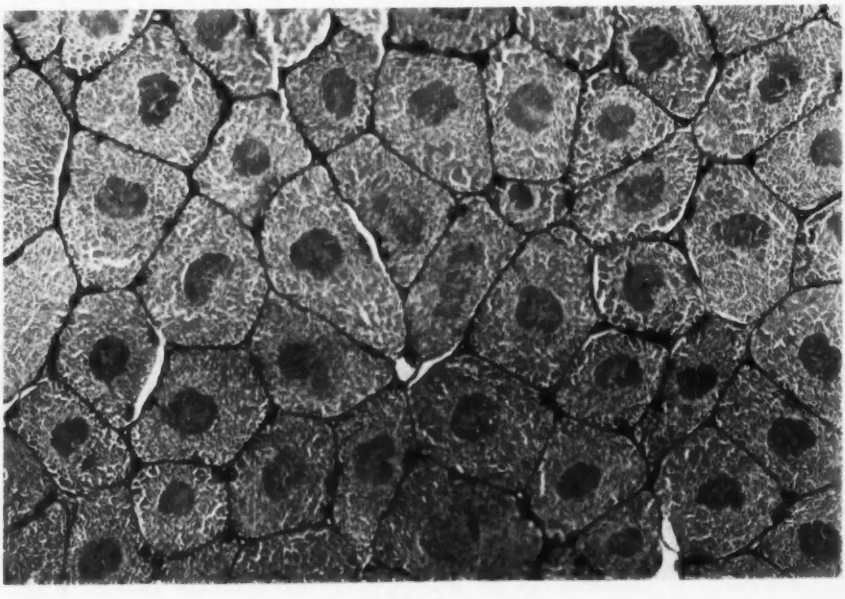

FIG. 9B.

To illustrate article by G. Milton Shy and Kenneth R. Magee.

PLATE L

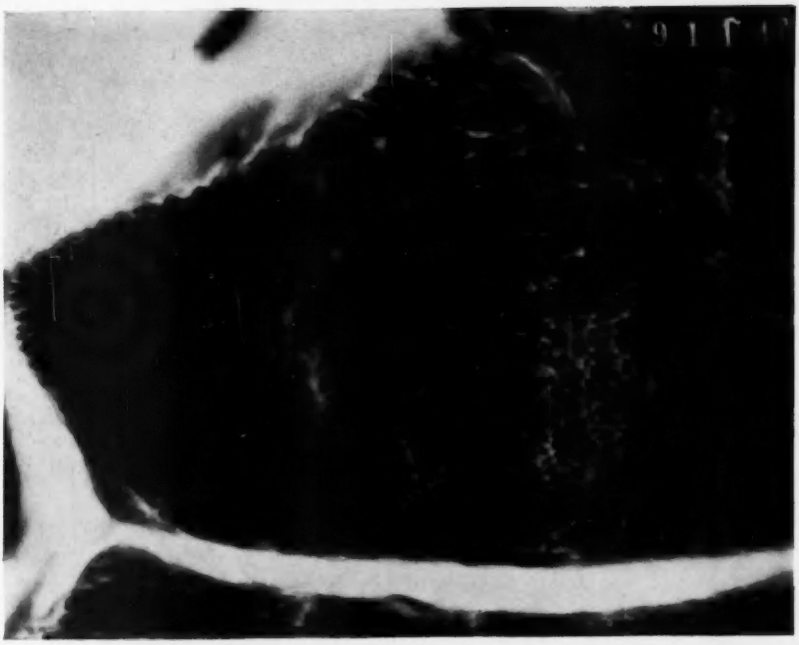

FIG. 10A.

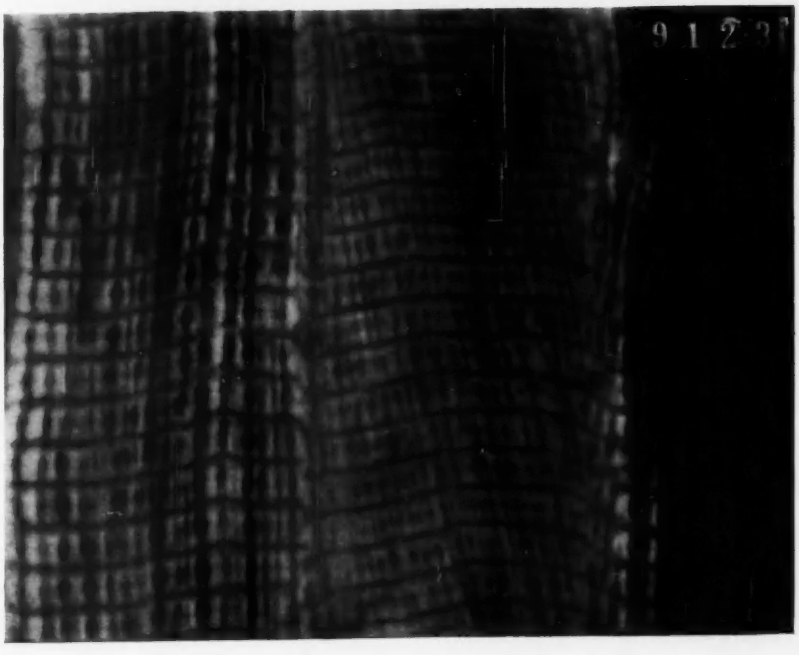

FIG. 10B.

To illustrate article by G. Milton Shy and Kenneth R. Magee.

PLATE LI

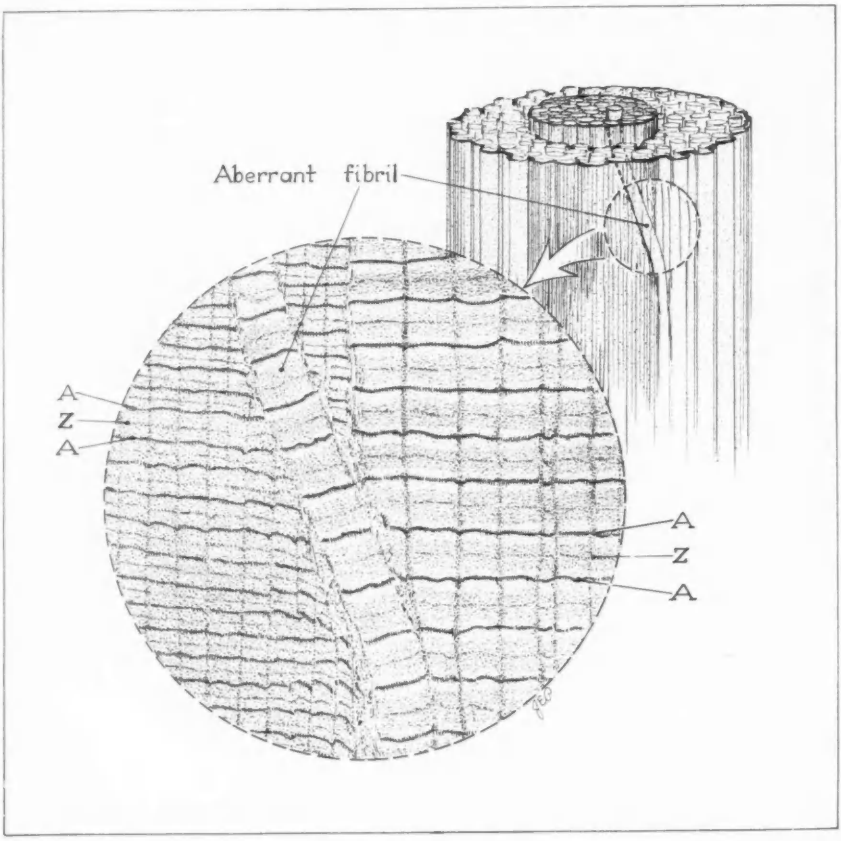

FIG. 11.

To illustrate article by G. Milton Shy and Kenneth R. Magee.

PLATE XLVIII

FIG. 8A (*Case* 5).—9151. Hæmatoxylin and eosin. × 850 (Bouin's). This is a polarized photomicrograph of a longitudinal fibre. Note the central fibrils have a different birefringence in the upper fibre.

FIG. 8B (*Case* 4).—9121. Gomori Tri-chrome. × 1,250 (Formol-saline). This longitudinal section of a single fibre shows the length of a sarcomere of the central fibrils to be different from that of the peripheral fibrils.

PLATE XLIX

FIG. 9A (*Case* 4).—9120. Gomori Tri-chrome. × 1,250 (Formol-saline). This single fibre shows aberrant fibrils from the periphery entering the abnormal central portion of the fibre.

FIG. 9B (*Case* 4).—9118. Periodic acid-Schiff after diastase. × 440 (Formol-saline). This low power field shows the central fibril to have a more positive PAS reaction than the peripheral fibrils. Since diastase was used, this colour difference is dependent on a substance other than glycogen.

PLATE L

FIG. 10A (*Case* 4).—9114. Gomori Tri-chrome. × 1,700 (Formol-saline). This cross section of a single fibre demonstrates the colour difference and anatomical changes present in the central fibrils.

FIG. 10B (*Case* 8).—9123. Gomori Tri-chrome. × 2,400 (Formol-saline). This is a longitudinal section through a portion of a single fibre. In this instance the sarcomere of the internal and external fibrils are of the same size. One may see that both the Z and A bands are continuous through the central fibrils.

PLATE LI

FIG. 11.—A diagrammatic reconstruction of a typical abnormal muscle fibre based upon multiple sections.

CYSTICERCOSIS OF THE POSTERIOR FOSSA

BY

EDWIN R. BICKERSTAFF, J. M. SMALL AND A. L. WOOLF

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INFESTATION of the human brain with the larval stage of the *Taenia Solium* has become so widely recognized in this country as a cause of epilepsy in individuals who have lived in India and the Far East, that very little attention has been paid to the strikingly different clinical manifestations which result when the parasite develops in the ventricular system or the basal cisterns.

This paper is based on our experience of the clinical syndrome produced by cysticercosis of the posterior fossa, and is an attempt to show how the condition may be recognized even when the characteristic features of the disease—epilepsy, mental deterioration, eosinophilia and calcification in muscles—are all absent.

In order to understand the mechanism of production of symptoms it is necessary to appreciate that, while the cysticercus which develops in the hemispheres forms a small, fixed, firmly encapsulated cyst, those which develop in the cerebrospinal fluid pathways may differ both morphologically and in behaviour. Several pathological forms are encountered:

(*a*) The single cyst, similar in every way to those seen in the hemispheres, but lacking at first the host capsule and therefore mobile, lying either in the third ventricle, aqueduct or fourth ventricle.

(*b*) The racemose cyst—a large, delicate, thin-walled, translucent, ramifying body, usually sterile, lying in the ventricular system, the cisterna magna, or the cerebellopontine angle, and even extending through the foramen magnum into the upper cervical region.

(*c*) A basal arachnoiditis, without any obvious cysticercus in immediate relationship.

(*d*) Any combination of the above.

The histology of the wall of the racemose cyst is highly characteristic and shows it to consist of three distinct layers:

(*a*) An outer wavy, acidophile, cuticular layer, about 3 μ in thickness, and showing a suggestion of cilia.

(*b*) A middle layer of rounded nuclei, varying in thickness, but usually 3–4 μ.

(*c*) An inner parenchymatous layer consisting of a reticulum of fine fibrils, with scattered rounded nuclei, and varying greatly in thickness, but rarely less than 40 μ.

A membrane histologically similar to this can be found lining many of the familiar intracerebral encysted cysticerci.

We have found the cardinal clinical features to be as follows:

(1) Attacks of intermittent obstructive intracranial hypertension, often precipitated by movements of the head, such as may be produced by any mobile body capable of blocking the intracranial cerebrospinal fluid pathways. These may be accompanied by gross signs of cerebellar disturbance and papillœdema.

(2) Marked disturbance of equilibrium—at first only during the attacks of obstructive hydrocephalus, but gradually becoming more permanent.

(3) Attacks suggestive of meningeal irritation or of meningo-encephalitis, in which the cerebrospinal fluid shows a pleocytosis, predominantly lymphocytic, a raised protein, normal sugar, but paretic Lange curve.

As the more familiar intramuscular and intracerebral cysticerci may co-exist, some of the well-known features of the disease may also assist in diagnosis, but they may be entirely absent.

Between April 1954 and October 1955 we have encountered seven new examples of this form of cysticercosis, four of which have been confirmed by operation or autopsy, and we include one earlier case.

Case 1.—*Solitary Cysticercus in the Fourth Ventricle.*

A. G. A Polish female aged 54. First seen at the Polish Hospital, Penley, on August 20, 1954, and admitted to the Midland Centre for Neurosurgery on October 2, 1954. Case No. 54/219.

For two and a half years this patient had suffered from attacks of intense headache, vomiting and drowsiness, each lasting from several hours to three days, and recovering spontaneously. Between these episodes she was normal, but during the headache she complained of tinnitus, vertigo and unsteadiness of gait. During one such attack her C.S.F. had shown 20 lymphocytes per c.mm.; 80 mg. protein per 100 ml. and a mild paretic Lange curve.

Examination carried out on a day when she had a severe headache showed her to be drowsy, confused and irritable. There was limitation of conjugate upward and lateral deviation of the eyes, gross nystagmus in all directions, but no papillœdema. The strength in the limbs was normal, all the reflexes were exalted but the plantars flexor. Both legs showed marked ataxia.

A few days later, when free from headache, re-examination was normal but for slight nystagmus on lateral gaze.

X-rays of the skull and the soft tissues of thighs, pelvis and chest wall, were normal. A full blood count was normal.

While waiting for further radiography using contrast media, the patient suddenly became deeply comatose and died within a few hours.

Pathology.—Autopsy performed October 5, 1954. Relevant macroscopic abnormalities were confined to the brain.

The brain was exposed by removing the calvarium including the occipital bone.

There was marked tonsillar herniation, and between the tonsils the choroid plexus of the fourth ventricle was extruded through the foramen of Magendie. The cerebral hemispheres appeared swollen and the intraventricular pressure was high. The floor of the third ventricle was thin, translucent and strikingly ballooned. Arising from the floor of the left middle fossa was a small, firm, sessile nodule, with a smooth surface.

The brain was sectioned in the mid-line in the sagittal plane (fig. 1). Above the mid-point of the fourth ventricle there was marked dilation of the ventricular system, the foramina of Monro measuring 1 cm. in their maximum diameter. The third ventricle was much enlarged, and the aqueduct grossly dilated, its upper opening measuring 0·5 cm. in vertical diameter, while the quadrigeminal plate appeared displaced backwards and upwards. The upper part of the fourth ventricle was grossly enlarged, but at its mid-point there was a small (0·4 cm. long) blood clot, adherent to the ependyma; posterior to the clot the floor of the ventricle was thickened by soft, whitish tissue, which became continuous with greyish, more translucent tissue adherent to the roof and covering the central white matter of the cerebellum. The fourth ventricle was completely divided into dilated anterior and collapsed posterior portions by this mass of tissue, which contained dorsally an elongated cavity 0·5 cm. in length and 0·1 cm. in breadth, lined by a thin layer of opaque yellow material. Within this cavity, on its posterior wall, was a whitish nodule resembling a grain of rice. The gross appearances suggested a cysticercus impacted in the fourth ventricle.

On the medial surface of the occipital lobe was a small nodule composed of chalky material surrounded by a thick fibrous capsule. There was a small firm nodule in the cortex of the left supramarginal gyrus, and other nodules in the putamen and caudate nucleus on the right.

Histological examination of a large block consisting of a parasagittal section through the aqueduct and fourth ventricle showed the cyst to be surrounded by a broad glial capsule, around which there was considerable demyelination, with pallor of myelin-staining extending into the white matter of the cerebellum. The capsule surrounded the invaginated body of a tapeworm larva (fig. 2), showing suckers and well-marked hooklets, some of which are in the process of being digested by leucocytes. The nodule in the supramarginal gyrus was examined histologically and shown to contain the hooklets and suckers of a degenerated tapeworm larva. The nodule from the middle fossa consisted of a dense fibrous capsule surrounding a necrotic centre. The only other feature of histological interest was a marked periportal polymorphonuclear infiltration in the liver, many of the cells being eosinophils.

Comment.—From the degree of encapsulation of this parasite it is clear that it could not have been mobile for some considerable time and yet produced attacks presumably of acute obstructive hydrocephalus. The irritative effect of its presence is shown in the C.S.F. findings and it is possible that local inflammatory or allergic changes were responsible for the transient obstructive symptoms, the final episode being a combination of complete obstruction and tonsillar herniation. A Torkildsen's operation should have produced considerable relief of symptoms.

Case 2.—Solitary Cysticercus in the Aqueduct: Racemose Cysticercus in the Cerebello-Pontine Angle.

A. M. Ukrainian male aged 55. First seen at the Polish Hospital, Penley, on

August 20, 1954, and admitted to the Midland Centre for Neurosurgery on September 13, 1954. Case No. 54/199.

For two and a half years this patient had been subject to attacks of intense headache, vomiting, tinnitus and vertigo, frequently brought on by abrupt movements of the head, and accompanied by marked ataxia of gait. These would last many hours and end spontaneously. He would then be normal until the next attack, except that for four months, on moving his head, he had had a curious sensation over the left side of the face, and twitching of the left facial muscles, while in the last two months he had become increasingly deaf in the left ear.

General examination was normal. In the central nervous system the fundi showed marked bilateral papillœdema of chronic type; there was nystagmus to right and left; and left-sided deafness. The left arm and leg showed a mild ataxia.

Examination during an attack of headache showed a great increase in the nystagmus; ataxia of both arms and legs; and a gross ataxia of gait.

Full blood counts were repeatedly normal. X-rays of the skull showed only general changes of increased intracranial pressure. EEG was normal. X-rays of thighs, pelvis and chest wall showed several ovoid, calcified bodies, having the appearances of cysticerci (fig. 3).

Air and Myodil ventriculography on September 22, 1954, showed dilatation of the ventricular system above the lower part of the aqueduct where the myodil was almost totally obstructed by a rounded body thought to be a cysticercus (fig. 4).

A posterior fossa exploration was then carried out, and, though the dura appeared unusually thickened in several places, there was no obvious abnormality on opening it; there was no pressure cone; the cerebellar tonsils and vermis were normal and the fourth ventricle appeared of normal size. The left cerebello-pontine angle was inspected and a strange, mucoid-like structure was seen lying wrapped around the fifth, seventh and eighth nerves. By gentle traction most of this (fig. 5) was removed, though its attachment extended forwards through the tentorial hiatus and was not identified. A Torkildsen's procedure was performed to combat the aqueduct obstruction.

The patient improved after this operation, and had no more attacks of headache and vomiting. His papillœdema slowly subsided; four months later he was able to return to work and two years later has remained perfectly well.

The histology of the material removed from the angle (fig. 11a) showed it to be a thin membrane, consisting of three distinct cellular layers as described earlier in this paper, and identical with the appearances of the wall of a racemose cysticercus.

Comment.—This case is an example of three different forms of cysticercus—calcified cysts in muscles, single cyst in the ventricular system and racemose cyst in the cerebello-pontine angle—occurring in the same patient and shows how, by the simple procedure of overcoming the obstruction in the aqueduct, the patient has been restored to full normal activity.

Case 3.—Racemose Cysticercus in the Fourth Ventricle and Cisterna Magna.

K. K. Polish male aged 48. First seen at the Polish Hospital, Penley, on September 17, 1954, and admitted to the Midland Centre for Neurosurgery on October 6, 1954. Case No. 54/230.

This patient had, for twelve months, suffered from attacks of intense occipital

headache with vomiting, lasting several days and ending spontaneously. During the attacks he could hardly see with his right eye, and his gait became grossly ataxic, this ataxia having been present in lesser degree in recent months even when he was free from headache. Movements of the head sometimes precipitated headache, and he suffered from occasional generalized convulsions and failing memory.

Examination when he was free from headache showed no obvious memory or speech defect. There was severe bilateral papillœdema with hæmorrhages, slight ataxia of the left arm, and mild ataxia of both legs with exalted tendon reflexes but flexor plantars. His gait was ataxic, with a tendency to fall backwards.

During an attack of headache he developed a coarse bilateral nystagmus and marked increase of ataxia in arms and legs. His gait became so unsteady that he could barely stand.

A full blood count and X-rays of the skull were normal, but the thigh muscles showed a few very faint ovoid opacities.

Myodil ventriculography showed a marked symmetrical hydrocephalus of the lateral and third ventricles; the aqueduct was not dsmonstrated but the fourth ventricle was dilated in its upper part and showed an irregular filling defect inferiorly. The Myodil, when it had escaped into the cisterna magna, was irregularly distributed (fig. 6).

A posterior fossa exploration was carried out on October 13, 1954. As soon as the dura was opened in the mid-line a white cyst prolapsed, suspended by a filamentous pedicle. When the dura was fully opened, creamy-white, almost mucoid material was seen floating in the cisterna magna. Much of this was removed. When the tonsils were separated to allow access to the fourth ventricle, a cyst was seen protruding from the ventricle, its tail extending into the interior. Gentle traction resulted in the successive appearance of a number of delicate translucent cysts (fig. 7), all joined to a common pedicle, the whole structure finally coming away completely in a cascade, followed by an immediate flow of C.S.F.

The patient progressed favourably for three weeks but then developed further signs of high intracranial pressure. A white blood count and cisternal C.S.F. examination showed both to contain over 1,000 eosinophiles per c.mm. Antihistaminic drugs were administered, with considerable improvement and deterioration as soon as they were discontinued. The posterior fossa was re-explored on December 22, 1954, when it was found that the cerebellar hemispheres had herniated into the dural incision, and many areas had become frankly necrotic. No block to C.S.F. flow was seen, but the patient deteriorated and following several generalized convulsions, died on December 24, 1954.

Pathology.—The material removed from the fourth ventricle and cisterna magna (fig. 7) consisted of three simple translucent thin-walled cysts measuring from 0·9 cm. to 1·4 cm. in diameter, and a more complex structure which had been divided into three parts during surgical removal. It consisted of a pedicle of milky-white material from which extended a number of small very delicate cysts attached by stalks at times so delicate as to be filamentous. At one end of one portion there was a thick opaque beige-coloured area measuring 1·4 cm. by 2·2 cm., and seen to contain a cavity, on the inner aspect of which was a small, sessile swelling, opaque and white, bearing on the side a deep groove and four shallow grooves radiating from a central depression.

Section through the wall of the cysts (fig. 11B) showed the trilaminar appearance described earlier in the text, and serial sections through the beige-coloured cyst showed the mural nodule to consist of finely-spun collagenous tissue surrounding a honeycomb of spaces which appeared to contain blood. This resembled the

body cavity of a degenerating tapeworm larva (fig. 8). No definite hooklets or suckers were seen.

At autopsy a number of nodules were palpable in various organs, and section of those under the serosa of the lesser curvature of the stomach and in the lesser omentum showed them to be encapsulated structures compatible with degenerated cysticerci. There were foci of fibrosis present in kidney, liver, lungs and spleen.

Comment.—This is an example of the racemose form of cysticercosis in which an actual parasite was discovered in the racemose body—a very rare finding. The interference with this structure resulted in an intense blood and C.S.F. eosinophilia, suggesting an allergic reaction—a theory further supported by the response to antihistaminic drugs.

Case 4.—*Racemose Cysticercus in the Cisterna Magna with Basal Arachnoiditis.*

A. S. English male aged 58. First seen at the Hereford County Hospital on November 5, 1954, and admitted to the Midland Centre for Neurosurgery on January 2, 1955. Case No. 55/1.

This patient had been in the Regular Army and served in India from 1920-1927. Since 1947 his work had been deteriorating but his family noted no physical disability until 1952 when he developed unsteadiness of gait, impairment of memory and obvious slowing of all mental processes. His unsteadiness progressed steadily until he was almost unable to walk, he had recurrent severe headache and vomiting and developed a coarse tremor of hands and legs. In the two years prior to admission he had five episodes of loss of consciousness, at least one of which was accompanied by a generalized convulsion.

On examination he showed a gross memory impairment, mainly for events of the previous five years, and some disorientation in time and place. There was early papilloedema; his arms showed a coarse tremor not altered by movement, and a mild cerebellar ataxia. There was a similar tremor in the legs, but the ataxia was more marked, and position sense was impaired. All tendon reflexes were greatly increased, but plantars were flexor. Equilibrium was grossly disturbed and gait too ataxic for him to walk unaided.

X-rays of the skull and soft tissues of thighs, pelvis and chest wall showed no abnormality. Full blood count, blood and C.S.F. Wassermann, and EEG examination were all normal. The C.S.F. was examined twice in the two months, on the first occasion was at normal pressure and showed 125 lymphocytes per c.mm. and 80 mg. of protein per 100 ml., and on the second occasion showed a pressure of 220 mm., 31 lymphocytes per c.mm. and 108 mg. of protein per 100 ml. The Lange curve was 5554432100.

A Myodil ventriculogram was performed on January 10, 1955, showing a marked dilatation of all ventricles, including the fourth, but no Myodil could be made to leave the fourth ventricle. A posterior fossa exploration was carried out later that day by Mr. R. C. Connolly.

When the dura was opened, the arachnoid over the cisterna magna was opaque and thickened. On incising this the cistern was seen to contain about ten small cysts varing in size from 3 mm. to 1 cm. in diameter, consisting of tissue resembling normal arachnoid and filled with clear colourless fluid. Several of these were joined by fine filaments; others appeared free (fig. 9). When the cysts had been removed, the pia covering the cerebellar tonsils and dorsum of the brain-stem was seen to be thick and opaque, and in places appeared calcified. The posterior inferior cerebellar arteries were clearly defined, but as they ran upwards there was a considerable amount of fibrosis between them so the outlet of C.S.F. through the

foramina of the fourth ventricle seemed to be completely obstructed. Incision of this revealed an enlarged fourth ventricle, which contained no cysts. The edges of the thickened tissue were stitched to the posterior surface of the tonsils in an attempt to secure a free opening from the ventricle.

The patient recovered from the operation, but remained for many days in a state of great apathy and drowsiness, from which there was a gradual improvement on antihistaminic drugs. Ten days after the operation he suddenly developed a macular skin rash accompanied by a blood eosinophilia of over 1,000 per c.mm. This cleared rapidly and the patient was transferred to the Hereford County Hospital, where he died suddenly of a pulmonary embolism three weeks after operation.

Pathology.—The material removed from the cisterna magna at operation (fig. 9), consisted of four large and six smaller pieces of milky-white, semitranslucent tissue, most of which had originally been part of one racemose body. The histology of the cyst wall showed the trilaminar appearance described earlier in the text, but there was more degeneration, the outer layer being less hyaline, and the middle layer less cellular than in the previous specimens (fig. 11c).

At autopsy there was considerable thickening of the arachnoid over the base of the brain, and a further collection of racemose cysts in the cerebello-pontine angle on each side extending along the fifth and eighth nerves towards their exit foramina.

Section of the brain showed a moderate hydrocephalus with a granular ependymitis of the lateral ventricles. Cysticerci were found in the digitate white matter of the medial aspect of the left frontal lobe, and on the medial surface of the right superior frontal convolution was a clearly encapsulated cysticercus (fig. 10). Histology of this showed the parasite to be very degenerate but the body cavity could still be defined. Small nodules compatible with degenerate cysticerci were also found in the kidneys and the pharyngeal tonsil.

Comment.—The mental deterioration, limb tremor, ataxia, fits, C.S.F. lymphocytosis and paretic Lange curve were all suggestive of G.P.I., but the gross disturbance of equilibrium and the papillœdema suggested a mid-line space-occupying lesion in the posterior fossa. The combination of the patient's past history and the C.S.F. changes were sufficient to raise suspicions of cysticercosis, but the diagnosis was proved only by surgical exploration.

Case 5.—Posterior Fossa Arachnoidal Cyst.

J. C. English male aged 47. Admitted to the General Hospital, Birmingham, on October 11, 1947, under the care of Dr. Ronald St. Johnstone. Case No. G.236472.

This patient had served in the Regular Army in India from 1920-1923, was known to have contracted tapeworm, and developed epileptic fits in 1923. Latterly these occurred only about once in twelve months.

For four months he had complained of recurrent intense frontal headache, radiating to the occiput and down the back of the neck, accompanied by vomiting.

On examination he showed neck rigidity and a positive Kernig's sign. There was marked bilateral papillœdema. The right lower limb was slightly weak and the plantar reflexes extensor. Repeated white blood counts were carried out, and on one occasion the eosinophil count was 511 per c.mm. The cerebrospinal fluid was repeatedly examined, the pressures being consistently over 300 mm., and the cell counts over 100 cells per c.mm. of which 10 per cent were polymorphonuclear.

The protein content ranged from 85 mg. to 130 mg. per 100 ml., and the Lange curve was 5543321000. W.R was negative. X-rays of thigh muscles showed numerous cysticerci.

He was admitted to the Queen Elizabeth Hospital, Birmingham, on February 27, 1948, for neurosurgical treatment.

A ventriculography on March 3, 1948, showed uniform dilation of the lateral and third ventricles, and air had entered the dilated upper end of the aqueduct.

A posterior fossa craniotomy was performed (J. M. S.). The pressure in the posterior fossa was very high and remained so despite ventricular tapping. When the dura was opened, the cisterna magna was seen to be replaced by a large tense arachnoid cyst which spread upwards over the vermis to about the mid-point of the sagittal plane of the cerebellar hemispheres. When this was opened, the posterior fossa became completely slack, and air and C.S.F. were seen issuing from the fourth ventricle which was in communication with the cyst.

The patient's post-operative progress was marked by a great lethargy and attacks of dizziness on moving the head. The papillœdema subsided gradually, but six months later he was still reported to be suffering from headache, and the posterior fossa decompression was said to be bulging.

Attempts to trace this patient's later course have failed.

Comment.—This patient was known to have cerebral cysticercosis, but the obstruction to C.S.F. circulation appears to have been due to a large arachnoid cyst, rather than to any racemose cysticerci. It is probable that this cyst formed as a result of inflammatory arachnoidal changes secondary to the infestation.

Discussion

It is the popular conception in this country that cysticercosis is likely to occur only in individuals who have been in India or the Far East, and its prevalence in certain European countries and in South America is often overlooked. The geographical incidence has been extensively recorded by Dixon and Smithers (1935), Trelles and Lazarte (1941) and Pinto Pupo and others (1945–6), and its importance in relation to this country reviewed by Bickerstaff (1955).

Particular attention is directed towards the paper by Stepien and Choróbski (1949) illustrating the high incidence of this condition in Poland. There is now a large community of natives of Poland and surrounding countries living in England and it is the policy of the Ministry of Health that their hospital care should gradually be taken over by British hospitals. Neurologists and neurosurgeons need therefore to bear this diagnosis in mind even though the patient has never been farther East than Eastern Europe.

Another popular misconception is that cysticercosis is acquired by eating measly pork. The intestinal tapeworm is, of course, acquired in this way, but it is by ingestion of the ova of a tapeworm that cysticercosis develops. The importance of this is that a food-handler who acquired a tapeworm in, for example, India, could infect many individuals who have never left this island.

The patients with the form of cysticercosis described in this paper have usually been thought to have a posterior fossa neoplasm, for there is no single clinical feature which differentiates this condition from any other cause of intermittent obstructive hydrocephalus. The key to the diagnosis lies in the clinical evidence of multiplicity of cerebral lesions, some at least of which are capable of causing intermittent blockage to C.S.F. pathways and a cellular response in the C.S.F. over a long period of time. Our first case was an exception to this, and the diagnosis was suggested merely on the grounds of intermittent hydrocephalus with a C.S.F. pleocytosis, in a patient from an endemic area. Case 2 had signs of multiple lesions within the skull and cysticerci in the muscles. Case 3 had the signs of intermittent C.S.F. obstruction, but also epileptic convulsions, which suggested further lesions in the hemispheres, and this also applies to Case 4. Case 5 was known to have cysticercosis before he developed signs of a posterior fossa space-occupying lesion.

The precipitation of attacks of obstructive hydrocephalus by movements of the head has long been recognized as a sign of a cysticercus in the fourth ventricle (Bruns, 1906) though any relatively mobile body in the same situation might be expected to produce the same syndrome. We wish to draw attention to the pain and twitching of the face on head movements suffered by Case 2, due to the racemose body amongst the nerves in the cerebello-pontine angle. We have since seen a further patient with identical symptoms to this, and with calcified cysticerci in the thighs, and another with the same symptoms and a high blood eosinophilia, from the same country, but have not yet proved the diagnosis by surgical exploration.

Ancillary investigations may or may not be of assistance. The value of the C.S.F. changes has already been mentioned, but these patients may present with considerable papillœdema and examination of the C.S.F. by lumbar puncture will not readily be undertaken. The value of searching past records has proved to be very great, for these patients have often been through several hospitals in the course of their illness, and at some time the C.S.F. has usually been examined.

Electroencephalography is of value only if it shows a cortical focal discharge in a patient who has otherwise a purely posterior fossa syndrome. X-rays of the skull rarely show calcified cysts and it is important to examine the thighs, pelvis and chest wall. In none of these cases was there a marked eosinophilia until after surgical exploration.

We have obtained most information from ventriculography with air or Myodil—this may not only demonstrate the site of the lesion but give a good indication of its nature. In Case 2 the cysticercus was demonstrated just rostral to the fourth ventricle; in Case 3 a rounded defect was seen within the fourth ventricle, and the distribution of the Myodil in the cisterna magna suggested that it lay in the interstices of a multilocular body such as

the racemose form; in Cases 4 and 5 there was clearly defined an obstruction to the roof foramina, such as might be caused by arachnoiditis. All showed generalized hydrocephalus.

The nature of racemose intracranial cysts has been the cause of much interest in South America and South Africa. The dog tapeworm *Multiceps multiceps* forms in its larval stage a very similar structure in the central nervous system in man and animals, and Becker and Jacobson (1951*a* and *b*) consider it, and not the *Tænia solium*, always to be responsible for racemose bodies of the type described here. This is a view held by many authors. The *Multiceps multiceps* forms not a cysticercus, but a cœnurus, however—the cyst containing not one single scolex, but many hundreds. We showed previously (Bickerstaff and others, 1952) that a patient with undoubted cysticerci in the hemispheres had a racemose body in the posterior fossa, and we stated our objections to their theory. Trelles and others (1952) supported our view, and we consider this present series to give further support.

In Case 2 a racemose body was present in the angle and calcified cysticerci in the muscles. The racemose structure from Case 3 contained one single, large, degenerate larva—quite clearly not one of the scores of microscopic scolices found in cœnuriasis (*see* Becker and Jacobson, 1951). There were also cysticerci elsewhere in the body. Case 4 had, as well as the racemose cyst in the cisterna magna, undoubted cysticerci in the frontal lobes.

The reason for the formation of such a racemose body has been discussed at length by Trelles and others (1952), who consider that the larva lives in a symbiosis with its cyst wall, and that on its death a disordered proliferation occurs, resulting in the large, sterile racemose body. If this is so it might explain the common absence of scolices in racemose cysticercosis, for death of the only larva would result in a sterile cyst, whereas, applying the same theory to coenuriasis, death of many larvæ could occur and still many hundreds remain.

We feel, however, that there may be a simpler explanation. A cysticercus developing in the substance of the brain causes a brisk host reaction, and the formation of a limiting capsule. In the freedom of the ventricles or the subarachnoid spaces, however, the growth may continue unchecked, and the flow of C.S.F. may influence the site of its development and the direction of its extension. A racemose cyst never forms in the brain itself, yet the presence of the larva in Case 3 and the similarity of the histology of the wall to the lining of the intracerebral cysts leaves little doubt that the racemose body is the cysticercus itself and not merely some arachnoidal reaction, as we suggested previously (Bickerstaff and others, 1952).

That the meningitic reaction may, however, cause a cyst formation without the presence of the racemose cysticercus is suggested by Case 5, where a large tense arachnoidal cyst was discovered, without any other

definite abnormality, but with C.S.F. changes typical of cysticercosis and proven cysticerci elsewhere. This parasite should be remembered as one possible ætiological factor in the formation of the posterior fossa subdural arachnoidal cysts which neurosurgeons encounter from time to time, usually without finding any clear explanation of their development.

The surgical treatment of the familiar intracerebral cysts has met with very limited success, as might be expected when one considers the multiplicity of the lesions. At first sight the posterior fossa forms would appear to offer greater hope of removal, and indeed the solitary intraventricular cysts can be removed with benefit to the patient, as shown by Arana and Asenjo (1945), or successfully by-passed as in our Case 2. We have not had the same success, however, with the racemose variety, for though the obstructing cysts were removed completely in Cases 3 and 4, and in the previously published case (Bickerstaff and others, 1952), each patient developed post-operatively an intense meningeal reaction, and all have died.

That this meningeal reaction is probably a hypersensitivity phenomenon is suggested by the appearance of a high blood and C.S.F. eosinophilia during this stage, and by the reduction of the intensity of the reaction by anti-histaminic drugs—though these failed to influence the downhill course.

During removal, some of the cysts were ruptured on each occasion, and it is highly probable that the escape of the cyst contents into the C.S.F. pathways was responsible for the subsequent events. When these structures are seen lying free in the cisterna magna, or when they can be pulled out so easily from the aqueduct and fourth ventricle, it is tempting to undertake this manœuvre, and there is no doubt that the increasing obstructive hydrocephalus demands surgical intervention. In our series, however, the case in which the least was done is the only one still surviving, and once the diagnosis is confirmed it is probably wiser to confine the surgical procedure to either a Torkildsen's operation or a third ventriculostomy. No other treatment at present exists and relief of obstruction by surgery offers the only hope for a patient who will otherwise either die, or be rendered blind and helpless by this distressing disease.

Summary

In addition to the well-known supratentorial intraparenchymal cysts, intracranial cysticercosis may result in small solitary cysts becoming impacted in the aqueduct or the fourth ventricle; a large racemose body forming in the basal cisterns or within the ventricles; and an intense basal arachnoiditis.

Five cases are described in clinical and pathological detail to illustrate each of these features, and to show how different varieties may occur in the same patient.

The clinical picture differs strikingly from the classical syndrome of

cerebral cysticercosis and most cases present as posterior fossa or intraventricular tumours.

The approach to the correct diagnosis is discussed, and the importance stressed of associating attacks of intermittent obstructive hydrocephalus and intermittent dysequilibrium, occurring over several years, with characteristic C.S.F. changes and the opportunity of contracting the infestation.

Theories of the origin of the racemose cysticercus are discussed. It is suggested that the large growth of the structure results from the absence in the C.S.F. pathways of a limiting host capsule, and its shape is influenced by the direction of the C.S.F. flow.

An allergic cause is suggested for the meningo-encephalitis, and reference made to treatment and prognosis.

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LEGENDS FOR PLATES

PLATE LII

FIG. 1.—Sagittal section of brain of Case 1, showing dilatation of third ventricle, aqueduct and upper part of fourth ventricle caused by cysticercus embedded at mid-point of fourth ventricle.

FIG. 2.—A, Section through cysticercus in fourth ventricle of Case 1, showing invaginated tapeworm larva (× 20). B, Higher magnification to show hooklets and suckers (× 95).

PLATE LIII

FIG. 3.—X-ray of thighs and pelvis of Case 2, showing three calcified cysticerci.

FIG. 4.—Air and Myodil ventriculogram of Case 2, showing dilated lateral and third ventricles, and partial aqueduct obstruction by a rounded body, presumed to be a cysticercus.

PLATE LIV

FIG. 5.—Racemose structure removed from the cerebello-pontine angle of Case 2. The white spots did not represent scolices.

FIG. 6.—Air and Myodil ventriculogram of Case 3, showing dilatation of lateral and third ventricle, rounded obstruction in lower part of a dilated fourth ventricle, and the dispersion of Myodil in the cisterna magna.

FIG. 7.—Racemose structure removed from the fourth ventricle and cisterna magna of Case 3. Portions detached from each other during removal. Note darker, more opaque body in right lower corner.

FIG. 8.—Section through the opaque body in fig. 7, showing it to consist of the degenerate body of a tapeworm larva.

PLATE LV

FIG. 9.—Racemose structure removed from cisterna magna of Case 4. Several portions detached from each other during removal.

FIG. 10.—Cysticercus on right frontal lobe of Case 4.

FIG. 11.—Histology of the wall of the racemose cysts, showing the three layers described in the text. A, Case 2. B, Case 3—this cyst wall had more papillary structure that the others. C, Case 4.

PLATE LII

FIG. 1.

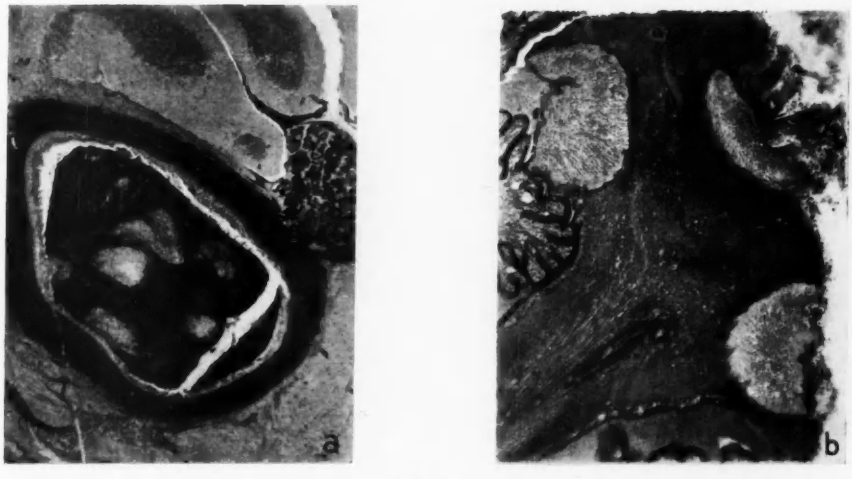


FIG. 2.

To illustrate article by Edwin R. Bickerstaff, J. M. Small and A. L. Woolf.

FIG. 3.

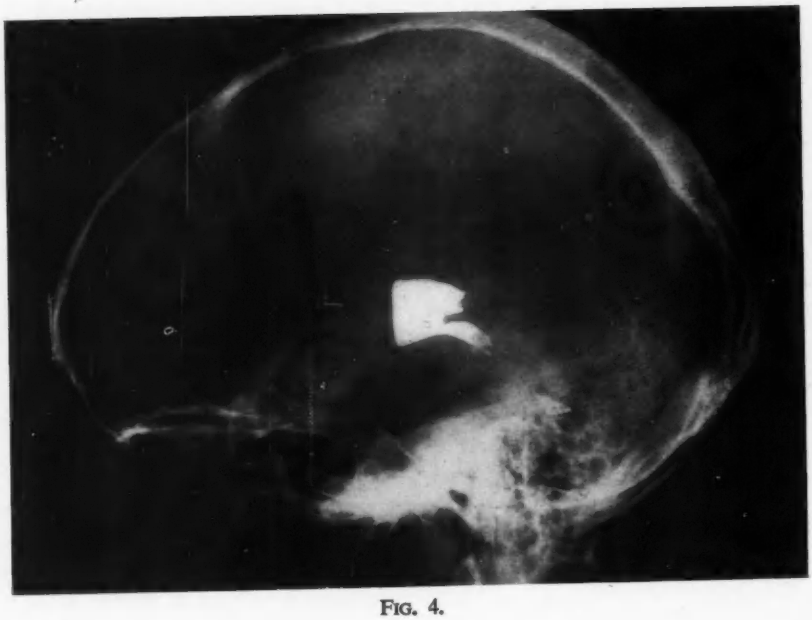


FIG. 4.

To illustrate article by Edwin R. Bickerstaff, J. M. Small and A. L. Woolf.

PLATE LIV

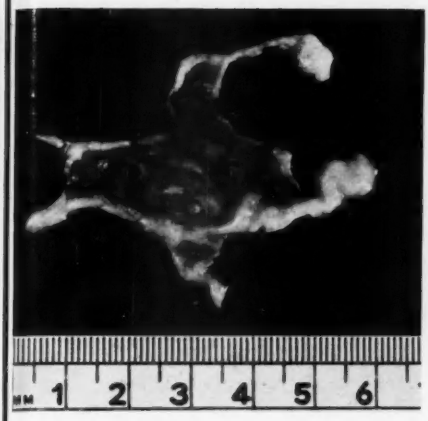


FIG. 5.

FIG. 6.

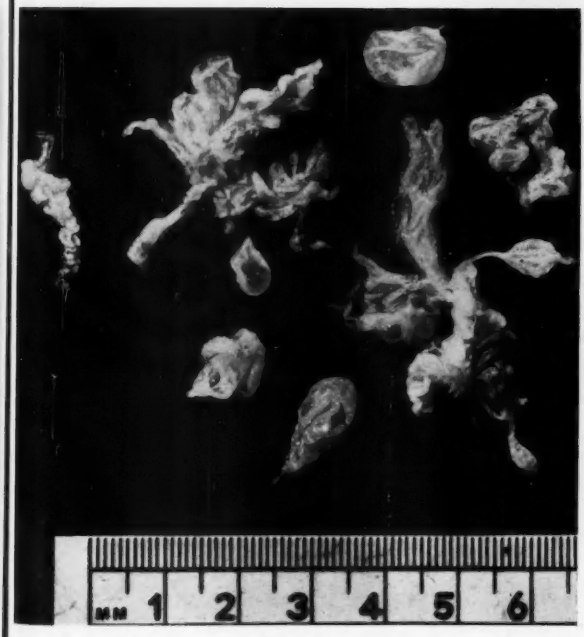


FIG. 7.

FIG. 8.

To illustrate article by Edwin R. Bickerstaff, J. M. Small and A. L. Woolf.

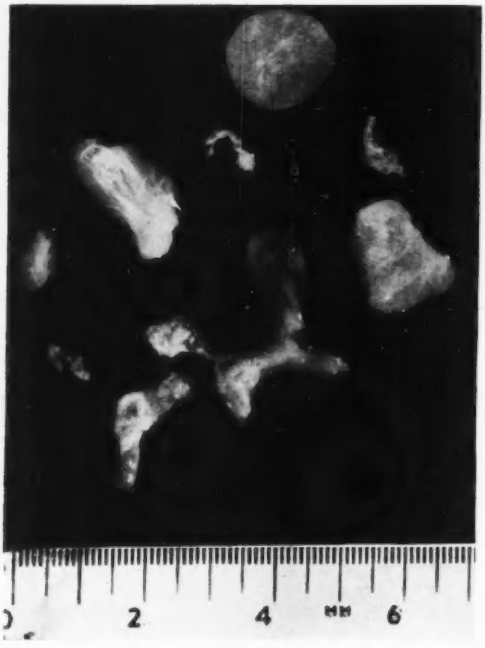


FIG. 9.

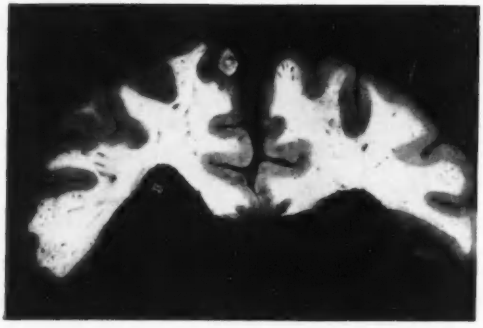
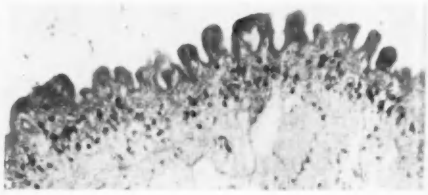
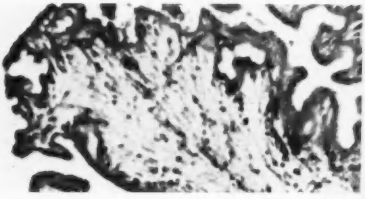


FIG. 10.





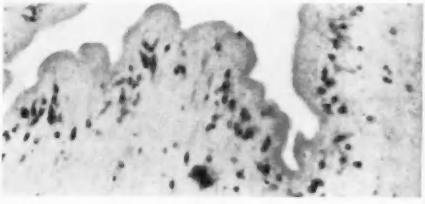


FIG. 11.

To illustrate article by Edwin R. Bickerstaff, J. M. Small and A. L. Woolf.

OBSERVATIONS ON THE PREVALENCE OF MULTIPLE SCLEROSIS IN NORTHERN SCOTLAND

BY

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ALTHOUGH multiple sclerosis is probably the most common organic nervous disease in Scotland, no accurate estimation of its prevalence exists. Figures based solely on hospital returns or mortality rates are subject to considerable error, and as emphasized by Allison and Millar (1954) the only sound method of estimating the prevalence of the disease is to determine the number of cases within an area and assess this in terms of the population.

The area selected in the present study comprises the counties of Shetland, Orkney, Caithness, Sutherland, Ross and Cromarty, Inverness and Nairn (*see* sketch map—fig. 1). The vast majority of patients with multiple sclerosis living in these counties has been interviewed and examined. In addition, the death-rate from the disease in Scotland has been ascertained and the results of an investigation into several factors which might be of ætiological importance are discussed.

Geographical note.—The region surveyed falls into three natural sub-areas:

(1) The Northern Isles (Shetland and Orkney).
(2) The Western Isles (Outer Hebrides; Skye).
(3) The Mainland Counties.

The Shetland Isles consist of some hundred isles and islets and extend approximately 70 miles from 59° 51′ N, and from 0° 45′ to 1° 45′ W. The population of 20,000 is confined to some twenty islands and more than half is contained on the principal island, Mainland, which exceeds in area all the other islands combined.

The general geographical relationship of the Shetlands is emphasized by the fact that Lerwick, the capital town, is about 210 miles north-north-east of Aberdeen and rather less than 200 miles west of Bergen in Norway.

Lying between the parallels 58° 41′ and 49° 24′ N latitude and 2° 22′ and 3° 26′ W longitude, some 50 miles to the south-west of Shetland, are the *Orkney Isles*. These consist of some 67 islands, of which approximately 30 are inhabited, the largest being Mainland.

FIG. 1.

Since both Shetland and Orkney lie in the course of the Atlantic Drift the climate is temperate. In Shetland the average maximum temperature is 48·8° F., and the average minimum 40·8° F., whilst in Orkney the temperature ranges from 38·5° F. in February to 53·5° F. in August. The rainfall, although not excessive (36–38 in.) is frequent.

The term "*Western Isles*" should properly be restricted to the Outer Hebrides, but, for the purpose of this investigation, Skye, correctly one of the Inner Hebrides, is included under this title. The Outer Hebrides—Lewis, Harris, North Uist, Benbecula, South Uist, Barra, lie off the north-west coast of Scotland at a varying distance of about 30 to 55 miles, and extend for approximately 120 miles from the Butt of Lewis in the north to Barra Head in the south. In addition to these main components, there are numerous small islets. Skye, with its attendant isles of Raasay, Rona,

Scalpay and Soay, is the largest of the Inner Hebrides, and has an area of 650 square miles. The rainfall of the Western Isles averages between 40 and 80 inches and the sunshine record between 1,200 and 1,300 hours.

The Mainland Counties in this survey comprise Caithness, Sutherland, Ross and Cromarty, Inverness and Nairn. The "highland line" is not a division between the north and the south of Scotland, but runs, rather, from the north-east in Sutherlandshire, south-west across the country towards Glasgow. The Lowlands lie east and south of this imaginary line, the Highlands to the west and north. Thus, Sutherland, Ross and Cromarty, and Inverness, are Highland counties, whereas Caithness in the far north-east is different geographically and racially, being flat instead of mountainous in contour, and Norse instead of Celtic in the origin of its inhabitants. The climate is also different, the rainfall in the extreme north-east varying between 30 and 40 in., whereas in the Highlands, 60 in., and even higher rainfalls may be recorded.

For purposes of local administration, Lewis forms part of Ross-shire; the remainder of the Outer Hebrides and Skye are included in Inverness-shire.

Generally speaking, there are few industries in this region, the majority of the inhabitants being engaged in agricultural pursuits, or in fishing. The census of 1951 (from which all figures of population in this communication are derived) indicates that the population in most districts has decreased. It is, therefore, probable that in the last twenty years any movement of population has been out of the region rather than into it.

Methods.—The investigation was started in 1951. A questionnaire was sent to all the practitioners in the region asking for the names and addresses of all cases suspected of suffering from multiple sclerosis in their practices and for permission to examine these patients in their homes or at the nearest clinic. In the event of no reply being received from a doctor within a reasonable time a reminder was sent and finally replies were received from all but two practitioners, a reply rate of 98·7 per cent.

All cases included in this survey have been seen personally. The patients on the mainland and in Skye were interviewed as opportunity presented; those resident in the Outer Hebrides were examined during September 1953, and those in Orkney and Shetland in May 1954. The information obtained was recorded on a specially constructed form and where possible hospital records were consulted to obtain serological and other data. The patients were thereafter placed in one of three categories:

(1) *Probable multiple sclerosis.*—Patients in whom the history, the results of clinical examination and, where available, hospital investigations, indicated that the diagnosis of multiple sclerosis was beyond reasonable doubt.

(2) *Possible multiple sclerosis.*—Patients in whom a diagnosis of multiple sclerosis appeared justifiable but in which the diagnosis could not be

established beyond reasonable doubt. Also included in this group are a few patients who did not wish to be examined, or who, for some reason, could not be seen. In these instances, scrutiny of hospital records suggested that the diagnosis was indeed multiple sclerosis.

(3) *Rejected cases.*—This group comprised patients found to be suffering from a disease other than multiple sclerosis.

The investigation was closed in October 1954, and patients seen during the course of routine work subsequent to this date have not been included in the report. Although it cannot be claimed that all cases of multiple sclerosis living in the region have been seen, I am satisfied that the investigation embraces the vast majority of those suffering from this disease.

It seemed desirable to compare certain particulars with information obtained from a control series of healthy people living in the same districts as the multiple sclerosis cases and belonging to the same sex and age groups. This was made possible by the willing co-operation of the Medical Officers of Health for the various counties, and by the district nurses who, in most instances, interviewed the people in the control series for me.

Analysis of water supplies in Shetland and Orkney for trace element content was undertaken by Dr. R. L. Mitchell of the MacAulay Institute for Soil Research, Aberdeen. Water rather than soil analysis was deemed desirable since at the present time food consumed even in rural areas is rarely derived from the soil of the district concerned. One gallon polythene containers were employed to transmit samples of drinking water from patients' homes, and from control areas to Dr. Mitchell's laboratory.

Information regarding diseases of animals was obtained from Dr. D. R. Wilson of the Animal Diseases Research Association, Moredun Institute, Edinburgh, and from Mr. P. L. Shanks of the North of Scotland College of Agriculture, Aberdeen, as well as from various veterinary investigation officers and practitioners.

The death-rate from multiple sclerosis was ascertained for each county in Scotland for the years 1931–1948. I am indebted to Mr. W. B. Fletcher, formerly of the Nuffield Bureau for Health and Sickness Records, Glasgow, who assisted me in this aspect of the investigation.

The Prevalence of Multiple Sclerosis

Notifications were received of 180 patients suspected of suffering from multiple sclerosis. After examination they were classified according to Table I. In 6 instances the patient had died in the interval between being notified and examined, and 4 patients had moved from the region. These 10 cases have been excluded from further consideration.

16 of the remaining patients were regarded as suffering from a disease other than multiple sclerosis. In this group were three brothers with familial spastic paraplegia. Other conditions misdiagnosed for multiple sclerosis were Parkinsonism (5), subacute combined degeneration of the cord (2),

TABLE I.—CLASSIFICATION OF CASES NOTIFIED AS SUFFERING FROM MULTIPLE SCLEROSIS

County	Multiple sclerosis: Probable	Multiple sclerosis: Possible	Dead or removed	Rejected	Total
Shetland	22	3	1	3	29
Orkney	17	6	4	2	29
Caithness	18	2	1	1	22
Sutherland	7	2	—	1	10
Ross and Cromarty ...	21	5	2	5	33
Inverness	38	9	2	4	53
Nairn	4	—	—	—	4
Totals	127	27	10	16	180

cervical spondylosis (2), motor neurone disease (2), spastic paraplegia of unknown origin (1), and spinal arteriosclerosis (1).

PREVALENCE BY COUNTIES

Table II indicates the prevalence of multiple sclerosis in the seven counties included in this survey. In a population of 231,116 the prevalence rate for probable cases only was 5·5 per 10,000, and for probable plus possible cases, 6·7 per 10,000. It will be observed, however, that the prevalence rate varies considerably from county to county. For example, the rate for Shetland was 11·3–12·9 per 10,000, whereas for Ross and Cromarty it was 3·4–4·3 per 10,000.

TABLE II.—PREVALENCE OF MULTIPLE SCLEROSIS

County	Population	Cases of M.S.: Probable	Cases of M.S.: Possible	Prevalence/10,000 of population: Probable	Prevalence/10,000 of population: Probable + Possible
Shetland	19,343	22	3	11·3	12·9
Orkney	21,258	17	6	8·0	10·8
Caithness	22,705	18	2	7·9	8·8
Sutherland	13,664	7	2	5·1	6·5
Ross and Cromarty ...	60,503	21	5	3·4	4·3
Mainland	36,771	17	4	4·6	5·7
Lewis	23,732	4	1	1·7	2·1
Inverness	84,924	38	9	4·5	5·5
Mainland	64,217	28	7	4·4	5·5
Skye	8,632	6	—	7·3	7·3
Harris					
N. Uist					
Benbecula ...	12,075	4	2	3·3	5·0
S. Uist					
Barra					
Small Isles ...					
Nairn	8,719	4	—	4·6	4·6
Totals	231,116	127	27	5·5	6·7

The distribution of cases at the time of the survey has been compared with the distribution by birthplace and at the time of the earliest symptoms of the disease. The results (Table III) indicate that the disease is more

TABLE III.—PREVALENCE OF MULTIPLE SCLEROSIS (PER 10,000 OF POPULATION) BY GEOGRAPHICAL DISTRIBUTION OF CASES

(probable cases only)

County	*Cases of multiple sclerosis*					
	At time of survey		*Birthplace*		*At time of onset*	
	No.	*Prevalence**	*No.*	*Prevalence**	*No.*	*Prevalence**
Shetland	22	11·3	20	10·4	18	9·3
Orkney	17	8·0	14	6·6	15	7·1
Caithness	18	7·9	17	7·5	11	4·8
Sutherland	7	5·1	1	0·73	4	2·9
Ross and Cromarty ...	21	3·4	13	2·1	14	2·3
Inverness	38	4·5	26	3·1	28	3·3
Nairn	4	4·6	2	2·3	—	—

* per 10,000 of population

prevalent in Shetland, Orkney and Caithness, compared with the other counties. Within the survey area, birthplaces other than the county in which the patients were examined show no particular trend. 4 cases were born in Inverness-shire, 2 in Caithness, 2 in Ross and Cromarty and 1 in Nairn. Patients born outside the survey area had their birthplace in various parts of Scotland, including Glasgow (6 cases) and Edinburgh (2 cases). 4 cases were born in England and 1 in North America.

A consideration of the place of onset in cases in which the initial symptoms occurred in a locality other than the county in which they were examined revealed no significant tendency. It is of some interest, however, that of the 127 probable cases the initial symptom was observed whilst the individual was serving in the Armed Forces in sixteen instances (12·5 per cent). In the majority the clinical onset occurred during service in temperate climates; in one case only did the onset occur whilst serving in the Far East. McAlpine (1946) noted the rarity of the disease among troops in the Middle East and India. I have not been able to trace any comparable comment on the incidence of the disease in members of the Armed Forces serving in Europe.

It is possible that the disease is present in the individual for some time before the first clinical manifestation occurs. Areas lived in for ten years before the onset were therefore studied, but no finding of significance emerged from this analysis.

PREVALENCE BY GEOGRAPHICAL AREAS

A classification of the prevalence of multiple sclerosis by counties is of limited value since county boundaries in many instances cut across geographical, geological and other natural borders. It has already been

mentioned that the survey area falls into three geographical subdivisions, and in Table IV the prevalence of multiple sclerosis in these areas is indicated. Particularly noteworthy is the prevalence of the disease in the Northern Isles (11·8 per 10,000 of population) compared with the Western Isles (3·8 per 10,000).

TABLE IV.—PREVALENCE OF MULTIPLE SCLEROSIS BY GEOGRAPHICAL SUB-DIVISION

Geographical sub-division	*Population*	*Cases of multiple sclerosis*		*Prevalence/10,000 of population*
		Probable	*Possible*	*Probable + Possible*
Northern Isles (Orkney and Shetland) ...	40,601	39	9	11·8
Mainland	146,076	74	16	6·2
Western Isles (Outer Hebrides, Skye) ...	44,439	14	2	3·8
Totals	231,116	127	27	6·7

PREVALENCE BY MORTALITY RATE

The mortality rate from multiple sclerosis was obtained from the Registrar-General's returns for each county in Scotland for the period 1931–1948. If the arbitrary figure of 20 years is taken as representing the average duration of the disease in this country (Allison, 1950; Pratt, Compston and McAlpine, 1951), the prevalence of multiple sclerosis can be obtained by multiplying the average death-rate per million by this figure. In this way the expected prevalence for each county in Scotland has been estimated and the results are indicated in fig. 2.

The expected and the actual prevalence of multiple sclerosis in the survey area is compared in Table V. It will be noted that with one excep-

TABLE V.—THE EXPECTED AND ACTUAL PREVALENCE OF MULTIPLE SCLEROSIS IN THE NORTHERN COUNTIES

County	*Expected prevalence by death-rate per 10,000 population*	*Actual prevalence per 10,000 population*	
		Probable	*Probable + Possible*
Shetland	14·8	11·3	12·9
Orkney	11·2	8·0	10·8
Caithness	6·2	7·9	8·8
Sutherland	9·0	5·1	6·5
Ross and Cromarty ...	6·0	3·4	4·3
Inverness	6·4	4·5	5·5
Nairn	11·4	4·6	4·6

tion (Caithness) the expected prevalence is greater than the actual prevalence. It is possible to explain this discrepancy partly by inaccuracies in diagnosis and certification, and partly by the assumption that some cases of the disease were not notified during the period of the survey.

FIG. 2.

In the survey counties, with a population of 231,000, there was a discrepancy of 23 cases between the expected and actual prevalence rates. A proportionate discrepancy for Scotland as a whole (population 5 million) would be 400 cases and it would therefore appear reasonable to assume a multiple sclerosis population in Scotland of between 2,500 and 3,000 cases.

OTHER FACTORS

Sex and age distribution.—In the United Kingdom there is a slight

excess of female over male patients, and in Scotland the sex rates for patients dying of multiple sclerosis is the same as that in the general population—1 : 1·08 (McAlpine *et al.*, 1955). This sex incidence is reflected in the present series; of the 127 probable cases, 71 were females (55·9 per cent) and 56 were males (44·1 per cent). This compares closely with the sex incidence found in an earlier series of 389 cases (Adams, Sutherland and Fletcher, 1950), and with the results of Allison and Millar (1954).

TABLE VI.—AGE AT ONSET IN 127 CASES OF MULTIPLE SCLEROSIS

	Years											
	<20		20–29		30–39		40–49		50+		*Totals*	
County	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Shetland	2	9·1	6	27·3	9	40·9	5	22·7	—	—	22	100
Orkney	—	—	6	35·3	8	47·1	2	11·7	1	5·9	17	100
Caithness	2	11·1	8	44·4	5	27·8	3	16·7	—	—	18	100
Sutherland	2	28·6	1	14·2	2	28·6	2	28·6	—	—	7	100
Ross & Cromarty	2	9·5	10	47·6	6	28·6	3	14·3	—	—	21	100
Inverness	1	2·6	11	28·9	16	42·1	8	21·1	2	5·3	38	100
Nairn	—	—	2	50·0	1	25·0	1	25·0	—	—	4	100
Totals	9	7·1	44	34·6	47	37·0	24	18·9	3	2·4	127	100

Table VI indicates the age distribution at the onset of the disease. 91 patients (71·6 per cent) were in the third and fourth decades of life.

The duration of the disease at the date of examination in 127 cases is outlined for each county in the survey in Table VII. Of these 127 patients,

TABLE VII.—DURATION OF THE DISEASE IN 127 LIVING CASES OF MULTIPLE SCLEROSIS

Duration years	*County*													
	Shetland		*Orkney*		*Caithness*		*Sutherland*		*Ross and Cromarty*		*Inverness*		*Nairn*	
	No.	%	*No.*	%	*No.*	%	*No.*	%	*No.*	%	*No.*	%	*No.*	%
0– 5	1	4·5	—	—	3	16·7	1	14·3	5	23·8	14	36·8	—	—
6–10	6	27·4	6	35·3	5	27·8	—	—	2	9·6	5	13·2	2	50·0
11–15	7	31·8	6	35·3	7	38·9	1	14·3	5	23·8	9	23·7	1	25·0
16–20	5	22·8	3	17·6	2	11·1	2	28·6	1	4·8	4	10·5	1	25·0
21–25	1	4·5	—	—	—	—	—	—	1	4·8	6	15·8	—	—
26–30	1	4·5	2	11·8	—	—	2	28·5	—	—	—	—	—	—
31–35	1	4·5	—	—	1	5·5	—	—	3	14·2	—	—	—	—
36–40	—	—	—	—	—	—	—	—	3	14·2	—	—	—	—
40+	—	—	—	—	—	—	1	14·3	1	4·8	—	—	—	—
Totals	22	100·0	17	100·0	18	100·0	7	100·0	21	100·0	38	100·0	4	100·0

23 (18·1 per cent) had suffered from multiple sclerosis for over twenty years and 15 (11·8 per cent) for over twenty-five years. With a few exceptions these patients were not severely handicapped. Allison (1950) in a follow-up of an unselected group of 40 cases first seen twenty-five years previously found that 28 had died, the average duration of the disease being approximately twenty years. In the Northern Ireland survey, Allison and Millar (1954) found that 54 (8 per cent) of their 700 cases had lived for more than twenty-five years.

Racial predisposition.—An ethnological discussion might appear out of place in a survey embracing a relatively small area and a population of only 231,000. It must be emphasized, however, that the disparity between the Northern Isles and the Outer Hebrides extends deeper than a geographical difference. McLaren (1951) states: " Not only is the Hebridean different from the Northern islander in race, temperament, blood, behaviour and often religion, but he has a different language; and his remoter history is one long story of the struggle between his forefathers and the forefathers of the Orcadians and Shetlanders."

In the eighth and ninth centuries the Norsemen colonized Shetland and Orkney in ever increasing numbers. Although in succeeding populations there may have been a strain of ancient Pictish blood probably from the distaff side (Fleur, 1953) these islands remained a possession of the Scandinavian countries until 1470 and in both Shetland and Orkney the Norse strain has survived. About the same time the mainland of Scotland adjacent to Orkney was colonized. As a result Shetland, Orkney and Caithness have now a population in which intermediate pigmentation of both hair and eyes predominates with fairly frequent segregation of pure blonde types. This is the commonest effect of crossing blonde blue-eyed stock with dark-haired brown-eyed stock (Hooton, 1947), and the non-Gaelic speaking, fair, blue-eyed inhabitants of Shetland, Orkney and Caithness present a marked contrast to the Gaelic speaking, darker haired Outer Hebridean and Highlander.

Although the Norse certainly colonized the Outer Hebrides and although Norse domination continued there until 1263, it is Celtic qualities which predominate in the main body of the Western islesmen. The Hebrides are the purest repositories of the Celtic tradition, the Celtic language and the Celtic way of life in all Scotland (McLaren, 1951). Although the physical characteristics of the Nordic are still obvious among some of the islanders this only serves to underline the predominate Celtic qualities of the vast majority of the Hebrideans.

Also predominantly Celtic are the Highland Counties of Sutherland, Ross and Cromarty, and Inverness. Although Skye is part of Inverness-shire its Norse associations are innumerable. According to MacGregor (1953) "one instantly feels oneself in a land where the Norse tradition rather than the Celtic predominates." This is not surprising when it is recalled that for centuries Skye was under the control of Norway, and although Gaelic speech is common, very few place names in Skye are not of Norse origin.

It is therefore possible to subdivide the survey region into a Celtic area comprising the counties of Sutherland, Ross and Cromarty, Inverness (Mainland), Nairn and the Isles of the Outer Hebrides, and a Nordic area which embraces Shetland, Orkney, Caithness and the Isle of Skye. An analysis of the prevalence of multiple sclerosis in these two areas

(Table VIII) indicates that the disease is twice as common in the Nordic as in the Celtic area. If the comparison is restricted to Shetland, Orkney and the Outer Hebrides, the difference in the prevalence of the disease is even more striking. The combined population of the Nordic Counties

TABLE VIII.—PREVALENCE OF MULTIPLE SCLEROSIS BY RACIAL AREAS

Area	*Population*	*Cases of multiple sclerosis*			
		Probable		*Probable + Possible*	
		No.	*Prevalence per* 10,000	*No.*	*Prevalence per* 10,000
Celtic area—					
Sutherland ... Ross and Cromarty Inverness (Mainland) Nairn ... ... Outer Hebrides	159,545	64	4·01	80	5
Nordic area—					
Shetlands ... Orkney ... Caithness ... Skye	71,571	63	8·8	74	10·3

of Shetland and Orkney is 40,601; the population of the Celtic Outer Hebridean isles of Lewis, Harris, North and South Uist, Benbecula and Barra is 35,595. In the Northern isles there are 39 probable cases of multiple sclerosis furnishing a prevalence rate of 9·6 per 10,000 inhabitants, whereas in the Outer Hebrides there are 8 probable cases, a prevalence rate of 2·2 per 10,000. If both probable and possible are considered the prevalence rate for Shetland and Orkney is 11·8 per 10,000 and for the Outer Hebrides, 3·1 per 10,000.

The Northern Isles and the Outer Hebrides are comparable in population and in their relative remoteness from the mainland of Scotland. Both areas were surveyed in the same way during a visit of approximately four weeks, and I have not, therefore, been more in contact with one area than the other.

Gaelic is, of cqurse, the original Celtic language, and it is apparent from Table IX that counties with a high percentage of Gaelic speakers

TABLE IX.—PREVALENCE OF MULTIPLE SCLEROSIS AND PERCENTAGE OF TOTAL POPULATION SPEAKING GAELIC AND ENGLISH

County	*Prevalence of multiple sclerosis per* 10,000 *of population (Probable + Possible cases)*	*% of total population speaking Gaelic and English**
Shetland	12·9	0·12
Orkney	10·8	0·24
Caithness	8·8	1·17
Sutherland	6·5	24·33
Ross and Cromarty ...	4·3	41·36
Inverness	5·5	27·86

* From the Census of Scotland, 1951.

have a low prevalence of multiple sclerosis. Finally, the high prevalence rate in Shetland and Orkney is reflected in the mortality rates for multiple sclerosis in these counties for the years 1931–48. Whereas the crude annual death-rate for Scotland as a whole was found to be 31 per million, the figures for Shetland and Orkney were 74 and 56 per million respectively. The corresponding figures for the counties of Ross and Cromarty and Inverness (which include the Western Isles) were 30 and 32 per million.

The familial incidence.—In the present investigation 127 patients were accepted as suffering from multiple sclerosis. These patients constituted the "index cases." 24 of the index cases reported that a relative had suffered or was suffering from the same disease (18·9 per cent). In 10 instances (7·9 per cent) although a diagnosis of multiple sclerosis appeared likely in the secondary cases, it was considered that insufficient proof existed and such index cases were classified as having a doubtful familial incidence. In 14 (11·0 per cent) of the index cases reasonable confirmation of the diagnosis was obtained by personal examination of the secondary cases or by a study of their case-histories and hospital records ("positive familial incidence"). The county prevalence of these index cases is indicated in Table X.

TABLE X.—FAMILIAL INCIDENCE OF MULTIPLE SCLEROSIS

	Cases of probable multiple sclerosis		*Familial incidence*			
		Prevalence	*Positive*		*Doubtful*	
County	*No.*	*per* 10,000	*No.*	%	*No.*	%
Shetland	22	11·3	4	18·2	1	4·5
Orkney	17	8·0	3	17·6	5	29·4
Caithness	18	7·9	2	11·1	1	5·5
Sutherland	7	5·1	—	—	—	—
Ross and Cromarty ...	21	3·4	1	4·8	1	4·8
Inverness	38	4·5	4	10·5	2	5·2
Nairn	4	4·6	—	—	—	—

It is apparent that the high prevalence rate of the disease in Shetland and Orkney is associated with a high familial incidence. It was therefore important to ascertain to what extent this last finding might be due to parental consanguinity. It was found that consanguinity occurred in only 2 of the 14 index cases (14·3 per cent) and in a further 3 cases the relationship of parents and grandparents was unknown but consanguinity was considered unlikely. This does not discount the possibility that parents and grandparents might be more remotely related and there are grounds for believing that a relationship of this nature obtains in several instances. The relationship of secondary to index cases can be summarized thus:

Relationship	*No. of cases*
Sibling	7
First cousin	2
Daughter	2
Second cousin	2
Niece	1

No example of conjugal multiple sclerosis was found in this investigation.

The number of near relatives at risk in the 127 probable cases of multiple sclerosis was found to comprise the following:

Grandparents	508
Parents	254
Uncles, aunts	1,303
Siblings	545
Sons, daughters	162
Total	2,772

The recognition of familial cases of multiple sclerosis occasions two problems:

(1) In surveys such as the present one the diagnosis in the secondary cases must be made on essentially clinical grounds.

(2) Should these patients indeed be suffering from multiple sclerosis as seems probable, to what extent does a familial incidence of 11·0 per cent suggest an inherited predisposition to the disease.

A characteristic feature of diseases of the nervous system is the similarity of clinical signs irrespective of the underlying pathological process. Most workers acknowledge the difficulties which can arise in this respect and the report of Fryer and Taverner (1953) emphasizes the tendency to diagnose sporadic cases of hereditary ataxia as multiple sclerosis. On the other hand, it is emphasized by McAlpine *et al.* (1955) that whereas multiple sclerosis is common the hereditary forms of spastic and ataxic paraplegia are rare.

Three brothers who were regarded as suffering from spastic paraplegia all had abnormal cardiograms. Evans and Wright (1942) established the high incidence of ECG changes in Friedreich's ataxia, and Roth (1948) noted the frequency of cardiac disease in the intermediate forms of hereditary ataxia. I have not been able to trace any literature suggesting that cardiac abnormalities occur with significant frequency in patients with multiple sclerosis nor do my own observations support such an association. It is therefore suggested that electro-cardiographic tracings may have an importance second only to examination of the CSF in establishing the diagnosis between multiple sclerosis and the hereditary ataxias when this is impossible on clinical grounds alone.

The second problem was to consider the extent to which a familial incidence of 11·0 per cent suggests an inherited predisposition to the disease. In the "probable" series (127 cases) 545 siblings and 162 children were at risk. Of these 7 siblings (1·3 per cent) and 2 children (1·2 per cent) were found to be suffering from multiple sclerosis. In a control series of 132 healthy people belonging to the same sex and age groups and living in the same geographical area there were 614 siblings and 214 children. No case of multiple sclerosis was found in this group. It therefore can be

assumed that the prevalence of the disease is considerably higher in the near relatives of cases of multiple sclerosis than in a control population.

Analysis of water supply.—Samples were obtained from the domestic water supplies of patients who had used the same source prior to the onset of the disease, and control samples were obtained from areas where there were no reported cases of multiple sclerosis. In the majority of instances the water supply was derived from surface wells and bacterial counts performed on several samples indicate heavy contamination with coliform micro-organisms.

TABLE XI.—TRACE ELEMENTS IN WATER SAMPLES: MICROGRAMS PER LITRE

Multiple sclerosis cases	*Co*	*Ni*	*Mo*	*Pb*	*Sn*	*Zn*	*V*	*Ti*	*Cr*	*Ag*	*Cu*
1 Sh.	10·4	7·2	0·3	<5	<4	215	0·6	5·5	0·9	<0·5	6·7
2 Sh.	<0·2	1·5	<0·2	<5	<4	39	0·3	<5	<0·5	<0·5	1·7
3 Sh.	<0·2	1·2	<0·2	<5	<4	<20	0·3	<5	0·9	<0·5	2·1
4 Sh.	0·3	2·5	<0·2	<5	<4	24	0·4	<5	0·8	<0·5	1·3
5 Sh.	0·4	11·6	<0·2	<5	<4	<20	0·2	<5	1·3	<0·5	2·7
6 Sh.	0·9	3·4	<0·2	<5	<4	24	0·4	<5	0·8	<0·5	2·5
7 Sh.	<0·2	4·8	<0·2	6	<4	19	0·2	<5	0·9	<0·5	2·1
8 Or.	<0·2	3·8	0·7	86	<4	83	0·5	<5	0·6	<0·5	18·2
9 Or.	<0·2	1·8	0·8	14	<4	550	0·3	<5	1·0	<0·5	6·1
10 Or.	<0·2	1·1	<0·2	<5	<4	1,310	0·4	<5	0·6	<0·5	0·8
11 Or.	<0·2	2·5	1·6	<5	<4	24	0·9	<5	0·7	<0·5	0·9
12 Or.	<0·2	13·6	0·4	<5	<4	24	0·6	<5	0·9	<0·5	1·0
13 Or.	0·3	1·8	1·7	8	<4	<20	1·7	10	1·1	<0·5	1·1

The results of spectrochemical analysis are detailed in Tables XI (multiple sclerosis cases) and XII (controls). Further analyses of the more major constituents (Ca, Na, K, Mg, Mu, Sr) were performed by a flame method. These results, not included here, showed no significant trend.

TABLE XII.—TRACE ELEMENTS IN WATER SAMPLES: MICROGRAMS PER LITRE

Control cases	*Co*	*Ni*	*Mo*	*Pb*	*Sn*	*Zn*	*V*	*Ti*	*Cr*	*Ag*	*Cu*
1 Sh.	1·6	12·1	<0·2	78	<4	79	0·5	<5	1·0	<0·5	197
2 Sh.	<0·2	0·8	0·8	<5	<4	110	<0·2	<5	<0·5	<0·5	3·0
3 Sh.	2·4	3·9	<0·2	<5	<4	<20	1·8	<5	1·5	<0·5	1·3
4 Sh.	<0·2	1·8	<0·2	<5	<4	<20	0·7	<5	1·1	<0·5	75
5 Sh.	0·3	2·5	<0·2	<5	<4	<20	0·3	<5	1·0	<0·5	2·6
6 Or.	<0·2	1·7	0·4	10	<4	<20	1·0	<5	1·0	<0·5	2·1
7 Or.	<0·2	1·1	<0·2	<5	<4	2,000	<0·2	<5	0·6	<0·5	1·5
8 Or.	<0·2	2·3	0·3	<5	<4	<20	0·6	<5	0·6	<0·5	0·7
9 Or.	0·4	10·3	<0·2	<5	<4	22	0·5	<5	1·0	<0·5	1·0
10 Or.	<0·2	8·1	<0·2	<5	<4	24	0·4	<5	0·8	<0·5	3·6
11 Or.	<0·2	28·6	0·4	47	<4	74	1·0	<5	1·1	<0·5	302·4

Allergy.—The prevalence of asthma, hay fever and urticaria in 39 cases of multiple sclerosis was estimated.

A family history of allergy was obtained in one-third of the multiple sclerosis cases and 5 (12·8 per cent) of the multiple sclerosis patients gave a personal history of asthma (2), urticaria (2) and hay fever (1).

These results suggest that allergic hypersensitivity is common in the families of multiple sclerosis patients, and multiple sclerosis patients themselves show a considerable tendency to develop generalized allergy.

Diet.—It has been suggested that dietary anomalies may account at least in part for the variable prevalence of multiple sclerosis. Williams (1947), for example, found low blood ascorbic acid levels in a series of multiple sclerosis patients and suggested that the high incidence of the disease in Norway compared with Mediterranean countries might be correlated with the scarcity of citrus fruits in Scandinavia. More recently, Swank (1950) and Swank *et al.* (1952) have sought to implicate a high dietary intake of animal and milk fat.

It was unfortunately beyond the scope of the present investigation to undertake exhaustive nutritional studies. A consideration of average diets in the Northern Isles, where the prevalence of multiple sclerosis is high, suggested that subclinical vitamin C deficiency might be fairly prevalent. On the other hand, a similar deficiency almost certainly exists in the Outer Hebrides where the prevalence rate is low.

The attitude of patients with multiple sclerosis towards dietary fat was compared with evidence obtained from control group in Shetland and Orkney with the following results:

	Likes fat in moderation		*Dislikes fat*		*Likes fat*	
	No.	*per cent*	*No.*	*per cent*	*No.*	*per cent*
Multiple sclerosis (39 cases)	9	23·1	14	35·9	16	41·1
Control series (48 cases)	13	27·1	15	31·2	20	41·7

Although a high dietary intake of animal fats might suggest a correlation with obesity, only approximately 5 per cent of multiple sclerosis patients were considered to be heavier than average compared with almost 15 per cent of the control cases.

Artificial feeding in infancy.—In a recent paper, Platt (1955) suggested that artificial feeding in infancy might play a part in the pathogenesis of multiple sclerosis. He suggests that babies fed on humanized cows' milk are relatively deficient in galactose which is necessary for the formation of galactocerebroside, one of the principal lipids of myelin. As a result, a glycocerebroside may occur for part of the galactocerebroside; should such an abnormal cerebroside persist into adult life it may determine a specific form of disease reaction.

The extent to which breast feeding had been practised in a series of multiple sclerosis cases was determined. In 75 cases the following results were obtained:

Breast fed	50 cases (66·7 per cent)
Bottle fed	18 cases (24·0 per cent)
Uncertain	7 cases (9·3 per cent)

10 of the breast-fed cases were unable to give information regarding the duration of this form of feeding. Of the 58 patients who could furnish adequate information, 37 (63·7 per cent) were breast fed at 3 months, 33 (56·9 per cent) at 6 months, and 5 (8·6 per cent) for periods in excess of 1 year.

In a control series of healthy people aged approximately 45 years and living within the survey region, approximately 75 per cent were breast fed and 25 per cent were bottle fed. Black (1955) has collected information covering practically every birth which occurred in Shetland during the years 1949–54 inclusive. In that county 70–75 per cent of the children were breast fed at 1 month after birth; 55 per cent at 3 months and 45 per cent at 6 months. Somewhat similar results were obtained by Douglas (1950) in his series of 4,669 infants, 53 per cent being breast fed at the second month and 36 per cent at the fifth.

Comment

The results of this survey indicate that the prevalence rate of multiple sclerosis in Northern Scotland is 5·5–6·7 per 10,000 of the population, and for Scotland as a whole a figure of between 5 and 6 per 10,000 was obtained by inference from mortality rates. Multiple sclerosis is thus the most common chronic organic disease of the central nervous system in Scotland and comparison with other surveys (Allison and Millar, 1954; Pratt, 1951) suggests that the disease is more common in Scotland than elsewhere in the United Kingdom.

A regional variation in the prevalence of multiple sclerosis reported from various continental countries (Bing and Reese, 1926; Ackermann, 1931; Gram, 1934; Sällström, 1942) was also encountered in this survey. The prevalence rate varied from 3·4–4·3 in Ross and Cromarty to the extremely high figure of 11·3–12·9 in Shetland.

The focal occurrence of multiple sclerosis in Scotland has been referred to in previous communications (Sutherland, 1950; Sutherland and Wilson, 1951), and in England Campbell *et al.* (1950) have described the occurrence of 6 cases in a Berkshire village. In this survey foci of high prevalence were encountered in Shetland, Orkney and Caithness. In addition I have knowledge of the disease affecting three girl friends, three neighbours living in the same street, and two gamekeepers who in succession lived in the same house. In none of these groups did any genetic relationship obtain.

The cause of regional variations in prevalence rates and the focal occurrence of the disease remains unexplained. This investigation has failed to furnish support for theories that have sought to implicate various dietary anomalies either in infancy or in later life. On prima facie grounds it seemed unlikely that artificial feeding would be practised extensively thirty to forty years ago in counties such as Shetland or Orkney. The

results of the enquiry substantiate this view and indicate that within the survey area artificial feeding in infancy was not practised more commonly in those who subsequently developed multiple sclerosis in later life than in healthy people; nor was the duration of breast feeding unduly short.

Although a relative dietary deficiency of vitamin C exists in nearly all expenditure groups in Scotland (Rowett Research Institute Report, 1955; National Food Survey Committee Report, 1955), this fact could not explain the disparity in the prevalence of multiple sclerosis in the Outer Hebrides compared with the Northern Isles. Similarly, no evidence has been obtained to support the view that a high dietary intake of animal fat is responsible for the frequency of the disease in Shetland and Orkney.

No known trace element deficiency was found to exist in the water supplies of patients suffering from multiple sclerosis living in Shetland and Orkney. It is apparent, however, that the metabolism of trace elements is extremely complex. Dick (1953), for example, found that the amount of inorganic sulphate in the diet of sheep influenced the storage of molybdenum, and this in turn of copper. It is possible that a similar mechanism could influence the utilization of copper or cobalt in the human.

It is generally agreed that there is a high incidence of multiple sclerosis in the Scandinavian states, and in the U.S.A. Bailey (1922) and Davenport (1922) found that the disease occurred with greater frequency in those of Scandinavian extraction than in those of other races. In this survey the prevalence of the disease was found to be much greater in the Nordic counties of Shetland, Orkney and Caithness than in the Celtic Outer Hebrides, and it is suggested that a disadvantageous genetic factor may exist in those of Nordic extraction.

That a genetic factor is operative in multiple sclerosis has been suggested by Pratt *et al.* (1951) and by MacKay (1950*a* and *b*). In the North of Scotland the overall familial incidence was found to be 11·0 per cent whereas the high prevalence rates in Shetland and Orkney were associated with a familial incidence of 18·2 per cent and 17·6 per cent respectively. The large number of unaffected relatives suggests, however, that there is no dominant mode of inheritance.

A high incidence of allergic disorders was found in the cases of multiple sclerosis and in their near relatives. This finding which is in accordance with the observations of others (Baer and Sulzberger, 1939; McAlpine, 1946; McAlpine *et al.*, 1955) suggests that in multiple sclerosis the reactivity of tissues tends to be altered. The known tendency for an exacerbation to occur after an infective illness, blood transfusion and, in some instances, protein shock therapy finds an explanation in the views of Urbach and Gottlieb (1946) and of Rich (1947) who have emphasized that although an organism may react at first only to a specific antigen, sensitization may

ultimately develop to a wide range of substances with the production of the same clinical picture as that produced by the original antigen.

The existence of an exogenous factor, either infective or toxic, would more readily explain both the regional variations in prevalence, and the focal occurrence of the disease, than any other single factor. The possibility that water supplies might be a source of infection cannot be disregarded. In the survey region, and particularly in Shetland, many homes still derive their domestic water supply from unfenced wells. This practice must have been even more prevalent in the past. The heavy bacterial counts in samples from some of these wells suggest that considerable seepage and contamination occurs.

Summary

(1) The population of the seven most northerly counties of Scotland is approximately 231,000. A survey in 1953 disclosed an over-all prevalence rate for multiple sclerosis of 5·6–6·7 per 10,000 of the population. In Northern Scotland approximately 1 in every 1,000 adults is affected by the disease, and in Scotland as a whole it was estimated that there is a multiple sclerosis population of between 2,500 and 3,000 cases.

(2) Within the survey area the prevalence rate varied from county to county and in Shetland the highest rate yet recorded in Great Britain was obtained (11·3–12·9 per 10,000). Within Counties the prevalence rate varied from district to district and in Shetland, Orkney and Caithness there was evidence suggestive of a focal distribution.

(3) Multiple sclerosis was found to be much more common in the Northern Isles (Shetland and Orkney) than in the Western Isles and it is suggested that a constitutional vulnerability exists in those of Nordic compared with Celtic extraction.

(4) A high familial incidence was obtained (11·0 per cent). This finding indicates that, although the disease is not purely genetically determined, a disadvantageous genetic factor exists.

(5) Factors such as trace element content of water supplies, dietary anomalies, artificial feeding and allergy were studied.

(6) There is a need for further and more widely planned surveys of multiple sclerosis in closed or semiclosed communities.

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HABITUATION OF THE AROUSAL REACTION

BY

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IF a drop of water falls on the surface of the sea just over the flower-like disc of a sea anemone, the whole animal contracts vigorously. If, then, a second drop falls within a few minutes of the first, there is less contraction, and finally, on the third or fourth drop, the response disappears altogether (Jennings, 1906). Here, in this marine polyp with the primitive nerve net is clearly exhibited one of the most pervasive phenomena of the animal kingdom—decrement of response with repeated stimulation. Almost every species studied, from amœba to man, exhibits some form of response decrement when the stimulus is frequently repeated or constantly applied (Harris, 1943). The ubiquity of the phenomenon plus its obvious survival value suggests that this kind of plasticity must be one of the most fundamental properties of animal behaviour.

It is hardly likely that the same mechanisms subserve response decrement in animals so morphologically distinct as the amœba, the sea anemone, and the higher vertebrates. Indeed, in animals possessing a synaptic nervous system, it is usually possible to distinguish several kinds of response decrement—sensory adaptation, nerve accommodation, effector fatigue, and what may be called "association fatigue" (Piéron, 1913), "internal inhibition" (Pavlov, 1927), "habituation" or "negative adaptation" (Humphrey, 1933; Hilgard and Marquis, 1940). Habituation (which appears to be a more neutral term than the others) like learning is clearly referable to some form of plasticity in the central nervous system, and, like learning, it has yet to be explained by any known neurophysiological principles. Habituation differs from both sensory adaptation and nerve accommodation in its temporal characteristics; it develops even when many minutes intervene between successive presentations of the stimulus and may persist for hours or even days. It does not depend on effector fatigue, since a response which has become habituated to a specific stimulus may still be elicited by an appropriate novel stimulus, whereas a fatigued effector will fail to respond, not only to the repeated stimulus, but to all other stimuli of the same relative intensity.

Such practically important phenomena as decrease of alertness during human watch-keeping, work decrement in monotonous tasks and boredom are demonstrably not due to effector fatigue or sensory adaptation, but rather to some form of habituation referable to the central nervous system (Mackworth, 1950; Bartley and Chute, 1947). Similarly, such obscure psychological phenomena as curiosity, the capacity of novel stimuli to capture attention and compel behaviour (Berlyne, 1951; Montgomery, 1953), insomnia produced by an unfamiliar environment, etc., seem to point to an initial sensitivity of the central nervous system to novel stimuli and a subsequent loss in sensitivity as the stimulus becomes familiar. Yet, despite the ubiquity of the phenomenon and its practical importance in human affairs, it has rarely been studied intensively from a neurophysiological point of view.

In studying habituation, we have given particular attention to the arousal reaction for several reasons: In the first place, it is reflected in readily recorded changes in the electrical activity of the brain—the "activation pattern" of Rheinberger and Jasper (1937). The large, slow rhythmic potential changes passing over the cortex during sleep are abruptly displaced by a rapid, low voltage discharge which may persist for many minutes after the termination of the arousal stimulus. Secondly, the neural mechanisms of arousal and wakefulness have been thoroughly investigated in recent years, work which has culminated in the present view of the brain-stem reticular system as essential to wakefulness and consciousness (cf. Adrian, Bremer and Jasper *Mechanisms and Consciousness*, 1954). A study of habituation of the arousal reaction should be interesting not only for its own sake but because of the light it may throw on the principles governing the sensitivity of the reticular system to afferent stimulation. Thirdly, the arousal reaction is known to habituate rapidly. Thus, Ectors (1936), Rheinberger and Jasper (1937), Clark and Ward (1945) and others, recording directly from the cortex of unanæsthetized animals, have observed that a clap or a whistle which is sufficiently intense to produce cortical activation and behavioural arousal loses this capacity when it has been repeated several times. Similarly, there is a decrement in the human alpha-blocking response to repeated stimuli (Knott and Henry, 1941), and Popov (1953) has reported that habituation of the alpha-blocking response may persist from one day to the next. Finally, the practical significance of habituation of the arousal reaction is evident in connexion with decrease of alertness during human watch-keeping, work decrement and similar phenomena.

Our experiments were designed to elucidate; firstly, the general properties of habituation—the duration of the state of habituation, its selectivity for specific stimuli, the interaction of stimuli to which the animal had become habituated with other, novel stimuli, etc.; secondly, the site and nature of the changes underlying habituation of the arousal reaction; and

thirdly, the principles governing the organization and sensitivity of the brain-stem arousal mechanism.

Material and Methods

Thirty-five cats were used. Multilead cortical plate and subcortical needle electrodes of the type devised by Delgado (1952) were permanently implanted with the usual aseptic precautions. The plate electrodes consisted of 3–5 stainless steel discs less than 0·5 mm. in diameter separated by distances of 4 mm. and embedded in a polyethylene plate. Plate electrodes were introduced through a small trephined hole over the posterior suprasylvian gyrus. The dura was slit and the polyethylene plate was slid rostrally under the dura until it lay over sensorimotor and frontal cortex. In some experiments, electrodes were also placed over auditory cortex, location of the electrodes being controlled by the cortical response to clicks as observed on a cathode-ray oscilloscope during the operation. Subcortical needle electrodes were oriented by means of a stereotaxic instrument, according the the atlas prepared by Jasper and Ajmone-Marsan (1955), and fixed to the skull by dental cement. Outside the cranium, wires from both plate and needle electrodes were encased in polyethylene tubing and tied to the skull by stainless steel wire. The tubing issued through a skin incision just over the occipital protuberance and terminated in a tiny polyethylene socket to which leads could be attached during recording sessions.

Cortical lesions were produced by aspiration, no effort being made to spare the white matter underlying the area to be destroyed. Subcortical lesions were produced by passing high-frequency current (500 kc) generated by a Wyss coagulator through electrodes orientated by means of the stereotaxic instrument.

Records were taken on an Offner six-channel dynograph at night when the laboratory was quiet and usually with the animal housed in its home cage in a sound-insulated room. Unless otherwise indicated, all the data reported below were obtained from bipolar recording techniques. Occasionally, when responses of auditory cortex were to be recorded, a cathode-ray oscilloscope was used and the tracings were recorded photographically. Each recording session lasted from four to ten hours, occurring from two days to six weeks following the implantation of electrodes, as many as ten sessions being devoted to a single cat.

Usually sounds were used as arousal stimuli. These were produced by a four-inch loud-speaker placed one to three feet from the animal and driven through a transformer by the output of a Grass (model S 4) stimulator. The absolute intensity of the signal was not measured, but the output voltage of the stimulator provided a rough measure of intensity within the frequency range used. A 500 cycle tone at 50 volts had a loudness of about 64 db based upon a human threshold of about 0·03

volt for this sound. In most experiments, sounds of at least this intensity were used. In some experiments, tape-recorded signals were used to avoid variation introduced by manual operation of the stimulator—particularly when "modulated tones" were to be presented, i.e. sounds which varied continuously in frequency, say, from 500 to 1,000 c/sec. in a period of four seconds. Experiments were designed to take account of possible differences in the intensity or "subjective loudness" of different stimuli.

The position of cortical electrodes was determined by inspection at autopsy. The position of subcortical electrodes and the site and extent of lesions were determined by examination of stained serial sections of the brain.

Results

In order to observe and compare the activation patterns produced by successive stimuli, it was necessary to establish a relatively persistent and stable synchrony in the electrical activity of the brain. This proved to be the greatest single technical problem confronted during this series of experiments. The use of sedatives and hypnotics proved impracticable, since it was impossible to maintain the delicate adjustment required over a sufficiently long period of time to compare the effects of successive stimuli. Consequently, all the data reported here were obtained during natural sleep without the aid of anæsthesia, sedation or restraint. After feeding the cat with warm milk, and seeing that it was comfortably housed in its home cage in the sound-insulated room, the experimenter simply waited until an appropriate degree of sleep was indicated by the electrocorticogram (Hess, Koella and Akert, 1953) before stimulating. This proved to be a workable procedure, although it was tedious and inflexible. The results of many recording sessions had to be discarded because of a failure to obtain the appropriate level of sleep.

The typical pattern of habituation obtained using this method is indicated by the following abstract of a protocol obtained from a normal cat two days after the electrodes had been implanted (*see* fig. 1):

After being fed with warm milk, the cat with leads attached was placed in the experimental room. Recording began about 8 p.m. During the first hour, the cat was restless, moved frequently, washed, etc., and, during this period, all channels showed very rapid activity with many movement artifacts. By 9.30 the cat had settled down, and occasional slow waves and spindles appeared in the electrocorticogram. A consistent sleep pattern lasting for many minutes did not appear until about 10.30.

The first stimulus, an intense (50 volts) 500 c/sec. tone of about 3 seconds' duration, was presented at 10.45. This aroused the animal, producing runs of activation in all channels which lasted slightly over 3 minutes (fig. 1, 1st tracing). Atypically, the first stimulus failed to produce overt

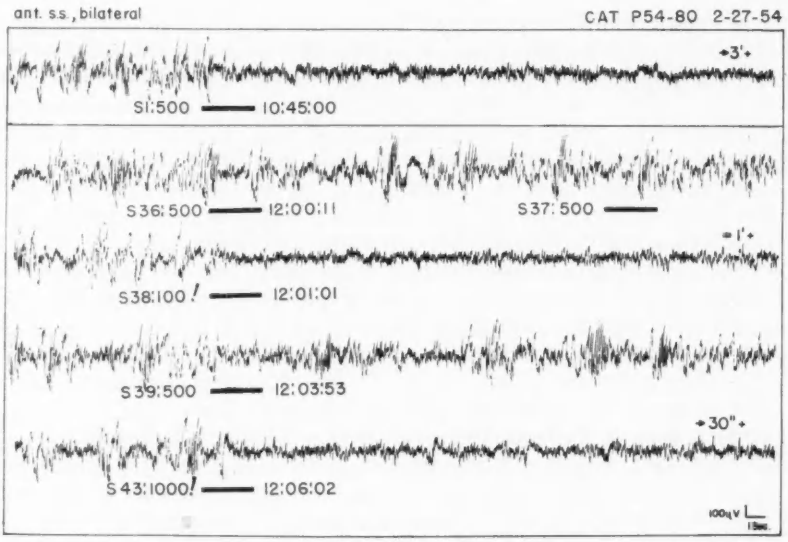

FIG. 1.—Cortical electrograms from the suprasylvian gyrus of a normal cat showing typical habituation of the arousal reaction to a 500 cycle tone after about 30 trials. In the first tracing the response to the first presentation of the 500 cycle tone is shown (S1 : 500). The solid bar shows the duration of the stimulus followed by the time in hours, minutes, and seconds (10 : 45 : 00). In the second tracing is shown the 36th and 37th trials (S36 and S37). Then a novel tone (!) of 100 cycles is presented in the 38th trial (S38 : 100!) followed by a repetition of the habituated tone (S39 : 500) and then another novel tone (S43 : 1,000!). The figures at the right above the E.E.G. traces indicate the duration of the activation in each trial.

movements. As soon as sleep patterns had returned to the electrocorticogram, the 500 c/sec. tone was repeated, and so on for many trials. The duration of activation patterns progressively decreased, rapidly during the first 10 trials and slowly and irregularly thereafter (Table I).

TABLE 1.—DURATION OF ACTIVATION PATTERNS PRODUCED BY THE FIRST TEN STIMULI DURING A TYPICAL RECORDING SESSION. TIME IN SECONDS.

Duration of activation	*Time since last stimulus*
192	0
100	220
210	337
30	262
15	112
19	90
5	69
75	115
12	182
7	32

During the period from 10.45 to 12.00, the stimulus was repeated 35 times. By the 30th trial, the animal had become more or less completely habituated to the 500 c/sec. tone, and subsequent presentations of this tone produced little or no alteration in the electrocorticogram (2nd tracing). After several repetitions of the 500 c/sec. tone failed to produce activation, a new tone (100 c/sec.) was presented. The animal was immediately aroused and remained awake for over a minute (3rd tracing). When sleep patterns had returned to the electrocorticogram, the familiar 500 c/sec. tone was repeated several times and consistently failed to produce arousal (4th tracing). On the 43rd trial, another novel stimulus—a 1,000 c/sec. tone—was presented. This too aroused the animal, producing runs of activation which lasted well over 30 seconds (5th tracing). Several subsequent presentations of the familiar 500 c/sec. tone failed to produce activation, and the recording session ended.

Changes in the activation pattern during habituation.—The habituation process seldom proceeded in a perfectly regular and consistent manner. Nevertheless, certain general changes in the activation patterns elicited by successive stimuli were commonly seen during these experiments: (i) The most striking and reliable change was a progressive decrease in the duration of activation. In all preparations, the period of activation decreased rapidly at first and then more slowly. After the first 5 or 10 presentations of an intense tone, the period of activation rarely lasted longer than 10 or 15 seconds. This remaining brief activation reaction, however, proved very resistant to habituation, as many as 20 or 30 trials being required before it disappeared entirely. (ii) As the stimulus was repeated, the time elapsing between the onset of the stimulus and the beginning of the activation reaction increased. Unlike the change in duration of activation, the increase in latency tended to occur slowly at first (perhaps 0·2 second in the first 10 trials). Later, after habituation had been partly established, the latency of activation varied greatly, and, occasionally, activation patterns might appear on the cortex as long as 10 or 20 seconds after the termination of the stimulus. Such enormous latencies were difficult to interpret, but the frequency with which they occurred in various experiments even when the record exhibited stable sleep patterns for many minutes preceding the onset of the stimulus convinced us that they were not due to coincidental associations between spontaneous arousal and the arousal stimulus. (iii) With the development of habituation, slow, large-amplitude waves and spindles tended to encroach on the activation pattern, so that the apparent flattening of the electrocorticogram became less marked with successive stimuli. Often, these slow waves occurred in such a way as to break the activation pattern into two phases.

Depth of sleep and speed of habituation.—It seemed quite clear that habituation required fewer trials during deep sleep. Moreover, there

was a tendency for the animal to fall more and more deeply asleep as the experiment progressed. This being the case, it was necessary to institute controls to make sure that the loss of responsiveness was due to an actual habituation process resulting from repetition of the stimulus and not simply to a spontaneous increase in the depth of sleep. When possible, the following controls were used: (i) Arousal stimuli were presented only when the electrocorticogram indicated fairly deep sleep (Hess, Koella and Akert, 1953). (ii) Stimuli were commonly used which were sufficiently intense to arouse the animal on their first occurrence regardless of the depth of sleep. The use of intense stimuli retarded habituation considerably, but if such a stimulus subsequently failed to produce arousal, one could be sure that the loss of responsiveness was due to repetition of the stimulus. (iii) Finally, if a novel stimulus of equal or less intensity aroused the animal after it had ceased to respond to a familiar stimulus, the effect could not be ascribed to an increased depth of sleep.

The inflexibility of our method, requiring as it did that the animal fall into a natural, spontaneous sleep before each stimulus was presented, prevented us from carrying out reliable, quantitative studies of the speed of habituation. However, the range of magnitudes encountered with the normal cat varied from 6 trials (click) to 60 (modulated tone—changing continuously in pitch from 500 to 1,000 c/sec. in a period of 3 seconds). In all preparations, modulated tones were more effective in producing arousal initially and more resistant to habituation than constant tones of the same or greater intensity.

It should be pointed out that the speed of habituation probably depends on the inter-trial interval as much as anything else. In our experiments, this interval varied from about 20 minutes to 20 seconds, dependent on the speed with which the animal returned to sleep after each arousal stimulus. The inter-trial interval usually became shorter as the experiment progressed.

Brain-stem activity during habituation.—In five cats, records were taken simultaneously from cortical and subcortical structures. In general, potentials led from mesial thalamus, posterior hypothalamus and mid-brain reticular formation were not strikingly different from those recorded from the surface of the cortex. In the alert waking state, both cortical and subcortical regions exhibited rapid, low-voltage activity, and during sleep the same regions displayed trains of slow, large-amplitude waves. Spindle bursts were less frequent in posterior hypothalamus and mid-brain reticular formation than in mesial thalamus and sensorimotor cortex, and the contrast between sleep and waking activity was not always as marked in the reticular formation as in the sensorimotor areas of the cortex. Occasionally, cortical activation patterns outlasted activation patterns recorded from deep structures by several seconds.

The results obtained during habituation may be summed up as follows: Wherever arousal was accompanied by flattening in the electrical activity of the brain, whether in cortex, diencephalon or mesencephalon, this flattening diminished and finally disappeared entirely as the animal became accustomed to the stimulus (fig. 5). During habituation, changes in activation patterns recorded from subcortical structures exactly paralleled changes in activation patterns recorded from the cortical surface.

Specificity of the habituation process.—If either the intensity or duration of a stimulus to which the animal had become completely habituated was increased, it became capable of arousing the animal. More interesting, however, was the specificity of the habituation process to the quality of the repeated stimulus. Thus, if the animal had become completely habituated to a repeated tone, it could still be aroused by a light touch, a change in illumination, or by a tone of a different frequency. In the protocol abstracted above, the animal had become habituated to a 500 c/sec. tone; yet a novel 100 or 1,000 c/sec. tone retained the capacity to produce cortical activation. Habituation in all normal animals exhibited at least this degree of specificity. There was, however, some generalization along the pitch continuum. If habituation to a 500 c/sec. tone had been established, a 600 c/sec. tone would usually be ineffective in producing arousal, and even a 1,000 c/sec. tone would have lost some of its initial effectiveness.

Habituation was occasionally specific not only to the pitch of a sound, but also to the arrangement of tonal elements within the sound—its pattern. This was demonstrated in the following way: A tape-recorded modulated tone (falling in pitch from 5,000 to 200 c/sec. in a period of 4 seconds) was repeatedly presented until the animal had become completely habituated (fig. 2). Then, by presenting the same sound in the reversed order (so that it rose in pitch instead of falling), the animal was exposed to a novel arrangement of the same tonal elements. This change in the pattern of the stimulus was sometimes sufficient to produce cortical activation even though the original stimulus, identical in frequency range, produced little or no alteration in the electrocorticogram. However, a change in the pattern of a stimulus after habituation was much less effective in producing arousal than a change in pitch. Pattern-specific habituation was not observed in all intact animals, and it was never observed in animals in which the auditory system had been damaged in any way.

Duration of habituation.—In discussing the duration of states of habituation it will be useful to distinguish between "phasic" activation patterns—those which barely outlast the stimulus—and "tonic" activaiton patterns, which may persist for many seconds or minutes. After an animal had become completely habituated to a repeated tone, the lapse

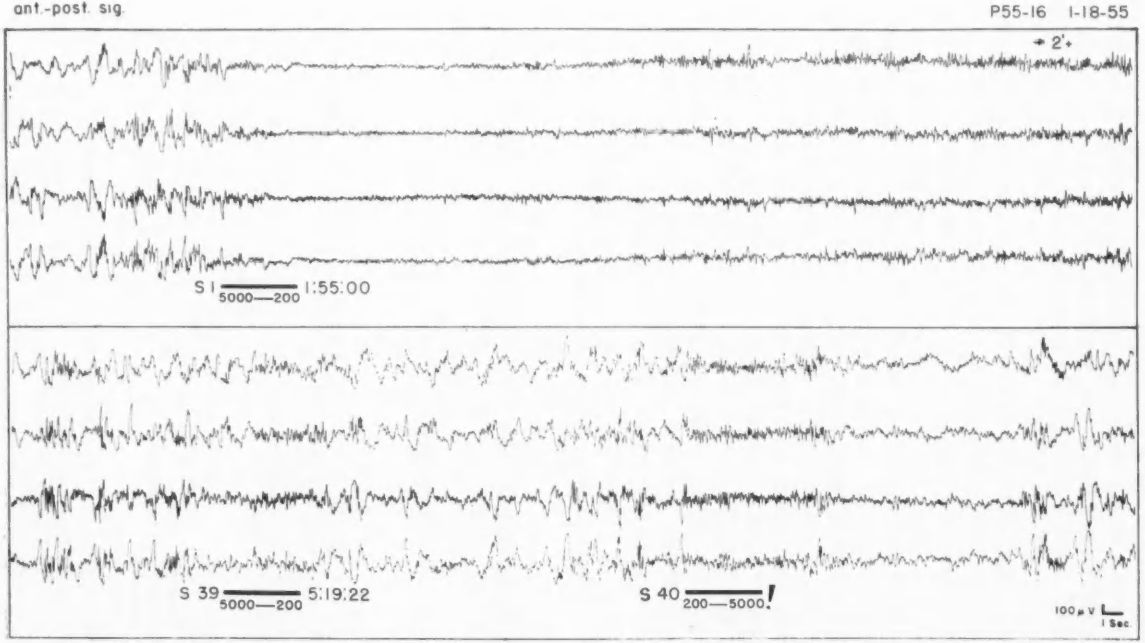

FIG. 2.—Habituation to a sound pattern consisting of a uniform "sliding" frequency change from 5,000 to 200 cycles shown in cortical electrograms from left and right anterior and posterior sigmoid areas. The first trial is shown in the first four tracings, habituation in the 39th trial below, followed by the same tonal sequence presented in the reverse order (S40, 200–5,000!) which acts as a relatively novel stimulus.

of a few minutes during which the tone was not presented would be sufficient to restore a phasic activation reaction. However, a quarter of an hour or more might be required before the stimulus regained its capacity to elicit a sustained, tonic reaction, dependent upon the number of times the stimulus had been presented during the experimental procedure.

We were struck by the fact that the animals seemed less responsive generally and became habituated more rapidly to experimental stimuli on the second and third days of recording than on the first. This seemed to indicate, at the very least, that a state of habituation to the experimental situation had developed which persisted from one day to the next. The effect was so marked in some cases that it was necessary to interpose several days' rest between successive recording sessions. Given such a rest, the animal's normal responsiveness was usually restored.

In another experiment, a 500 c/sec. tone was sounded every quarter of an hour for about ten days. Then two days were allowed to elapse during which the cat was not exposed to the stimulus. The first occurrence of the familiar 500 c/sec. tone produced a rather poorly differentiated phasic reaction lasting not longer than 15 seconds (1st tracing). The first occurrence of a novel 100 c/sec. tone, on the

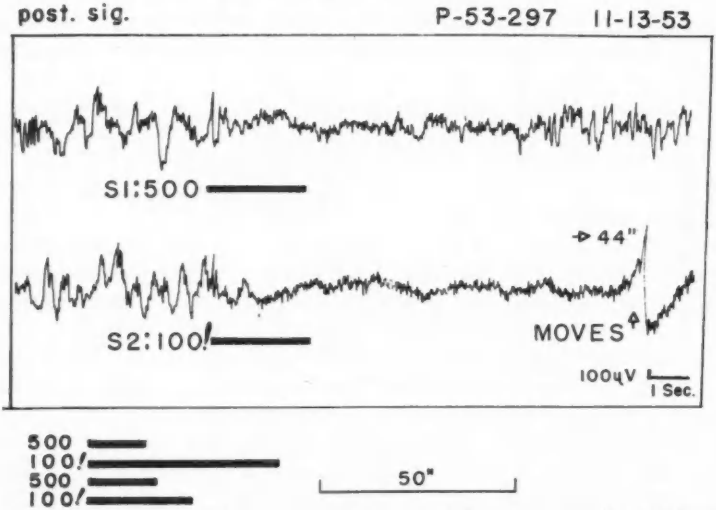

FIG. 3.—Illustration of degree of persistence of frequency-specific habituation in animal with bilateral ablation of auditory cortex (P53-297, fig. 6). In the first trace is shown the brief response to a previously habituated 500 cycle tone following a two-day rest period. The second trace shows the much longer response to a novel 100 cycle tone. Graphic representation of the duration of response to the first four stimuli following the two-day rest period is shown below.

other hand, awakened the animal completely, producing a tonic activation pattern lasting over 15 minutes (2nd tracing). Normally, a 500 c/sec. tone is slightly more effective in producing arousal than a 100 c/sec. tone—certainly not less so. With repetition, the 100 c/sec. tone rapidly lost its initial advantage and this advantage was never recovered even after a rest period. The long-lasting state of habituation generalized very rapidly to include the 100 c/sec. tone and remained general throughout the experiment (which was continued for several days). In fig. 3 is shown a similar long-lasting habituation in an animal with bilateral dilatation of auditory cortex.

Inhibition and disinhibition.—In the classical studies of conditioning, it was observed that the frequent repetition of a conditioned stimulus without reinforcement often led to drowsiness and sleep. Pavlov attributed this effect to an inhibitory process—the repeated stimulus acquiring the capacity to inhibit the activity of the hemispheres (Pavlov, 1927). The possibility that the Pavlovian hypothesis of internal inhibition applies to the habituation of the arousal reaction was tested in the following way: After the animal had become thoroughly habituated to a loud 500 c/sec. tone, this tone was presented simultaneously with a puff of air delivered through a glass tube taped to the animal's back. If the familiar tone caused a generalized inhibition to be exerted on the arousal mechanism or the cerebral hemispheres, the activation pattern

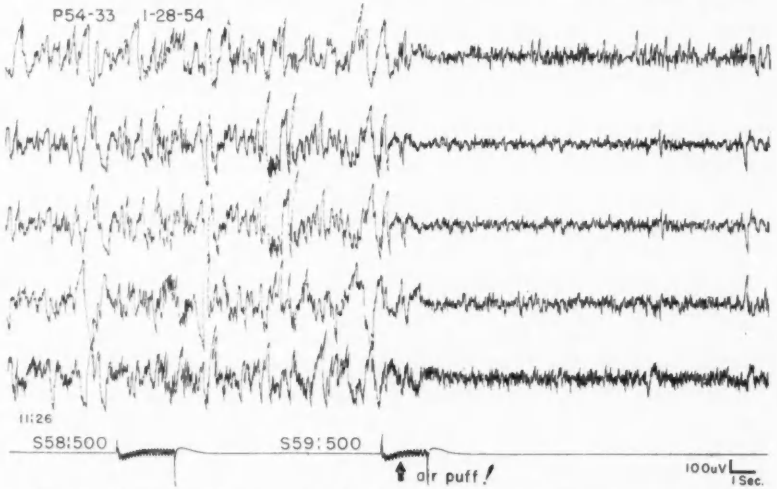

FIG. 4.—Generalized activation of the cortical electrogram from sigmoid and suprasylvian areas bilaterally is produced by a novel tactile stimulus (air puff!) when presented simultaneously with a tone to which the animal had been thoroughly habituated in 58 trials (S58:500). This illustrates lack of general inhibition in the habituation process.

produced by the novel but weak tactile stimulus should have been suppressed. However, as fig. 4 shows, if there was any interaction, it was one of summation rather than inhibition. Similar results were obtained when two tactile stimuli were used.

Pavlov also observed that the sudden introduction of an unfamiliar stimulus into the experimental situation might restore temporarily an extinguished response. In accordance with his belief that extinction depends on an inhibitory process, he referred to the momentary revival of an extinguished reflex by an irrelevant, novel stimulus as "disinhibition." Disinhibition (or "dehabituation" as it has sometimes been called) is frequently seen after the habituation of unconditioned reflexes in vertebrates. It has been reported after habituation of the withdrawal reflex in turtles (Humphrey, 1933), after habituation of the startle reflex in rats (Prosser and Hunter, 1936) and after habituation of the eyelid reflex in man (Oldfield, 1937).

It seems likely that the "disinhibition" of extinguished reflexes by novel, irrelevant stimuli depends on the potent non-specific activating effects of these stimuli, not on the blocking of some internal inhibition as the term implies. This interpretation is supported by the fact that disinhibition was seldom observed in the present experiments if the arousal effects of the novel stimulus were allowed to wear off completely before the familiar stimulus was repeated. Thus, in the protocols abstracted above, after the animal had become completely habituated to a 500 c/sec. tone, a novel 100 c/sec. tone was presented which produced a brief run of activation. When the animal had returned to sleep, the familiar 500 c/sec tone was still incapable of eliciting arousal. The process of habituation to a 500 c/sec. tone was not reversed by the introduction of a novel stimulus. Many times, however, we observed that a familiar stimulus which was by itself incapable of producing arousal might intensify the level of activation if it were presented while the animal was still partly aroused by the effects of a novel stimulus.

The activity of auditory cortex during habituation.—In investigating the site of the change on which habituation of the arousal reaction depends, we naturally considered first the primary sensory pathways. Recently, Hernandez-Peon and Scherrer (1955) and Galambos, Sheatz and Vernier (1956) have shown that when click stimuli are presented continually at intervals of 1–3 seconds over a period of hours or days, evoked potentials recorded from the cochlear nucleus and auditory cortex diminish in size. It is possible, therefore, that habituation of the arousal reaction depends on a change in the primary sensory pathways, that signals entering these pathways are damped or inhibited before they reach either the arousal mechanism or higher auditory centres.

This possibility was investigated by recording primary responses from auditory cortex during habituation of the arousal reaction. A series of

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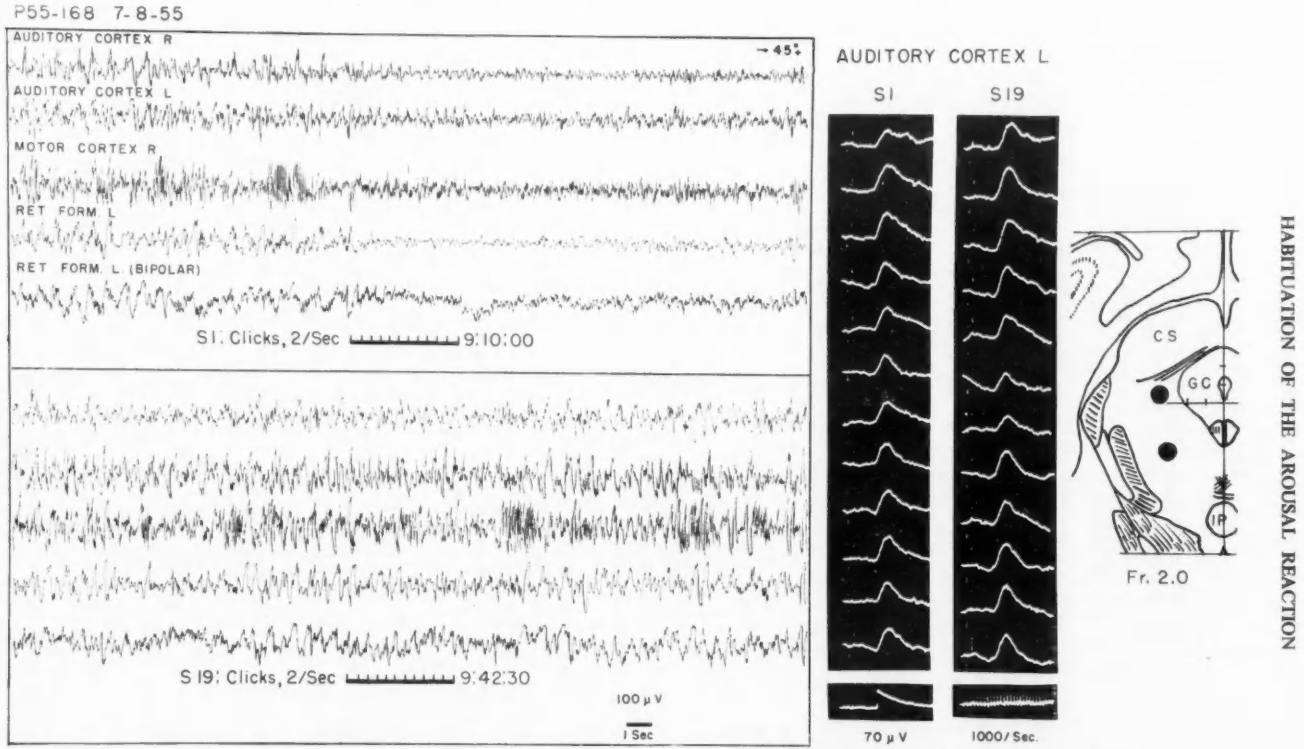

FIG. 5.—Cortical electrogams together with electrograms from the mid-brain reticular formation (*see* diagram at right) showing general activation response to auditory clicks at 2/sec. together with oscilloscope records of evoked potentials from auditory cortex (S1). After habituation (S19) of the activation response, evoked potentials are slightly increased.

12 clicks, 2/sec., was used as the arousal stimulus. Thus, a single arousal stimulus consisted of a train of 12 clicks lasting altogether about 6 seconds. Following the usual method, this stimulus was repeatedly presented at varying intervals until it no longer produced activation patterns. If habituation of the arousal reaction depended on the establishment of a block in the primary sensory pathways, we should expect to find evoked potentials recorded from sensory cortex diminishing in size or increasing in latency or both as the stimulus lost its power to produce generalized activation. However, this was not the case. There was no change in latency (about 8 msec.). The size of the potentials did change, but not in the predicted direction. Rather than diminishing as habituation of the arousal reaction developed, the size of evoked potentials increased. The results from one such experiment are shown in fig. 5. In this experiment, the potentials increased from a mean size of 98 μv. before habituation to 108 μv. after habituation. The probability that this increase was due to chance variation was computed and found to be quite small ($p < .02$ using the standard t-technique for testing the significance of differences between means).

Thus, we cannot attribute habituation of the arousal reaction to the establishment of a block in the primary sensory pathways. That such a block may be established by prolonged, continual stimulation at short inter-trial intervals has been shown by the experiments cited. But it cannot play a necessary role in habituation of the arousal reaction. The latter occurs even when many minutes intervene between successive presentations of the stimulus, it may persist for hours or days in the absence of stimulation, and it is accompanied by an increase rather than a decrease in the size of the primary response.

Why the primary cortical responses increase in size during habituation of the arousal reaction is an interesting question. It is unlikely that the habituation procedure itself produces the increment. After habituation, the stimuli fail to arouse the animal so that the primary responses are recorded against a background of sleep activity, and evoked potentials tend generally to be somewhat larger during sleep and anæsthesia. Direct stimulation of the brain stem reticular formation, producing the electrical changes associated with alert wakefulness, is known to result in a diminution of the amplitude of potentials recorded from afferent tracts in the cord and from other afferent structures including the cochlear nucleus (Kerr and Hagbarth, 1954; Hernandez-Peon and Scherrer, 1955; Galambos, 1956). In our experiments, if clicks at 2/sec. were presented continually *to the waking animal*, the evoked potentials recorded from auditory cortex disappeared occasionally for 2 or 3 seconds at a time. This tended to occur at moments when the animal was quite active. We considered and rejected as unlikely the possibility that the momentary disappearance of evoked potentials was an artifact produced

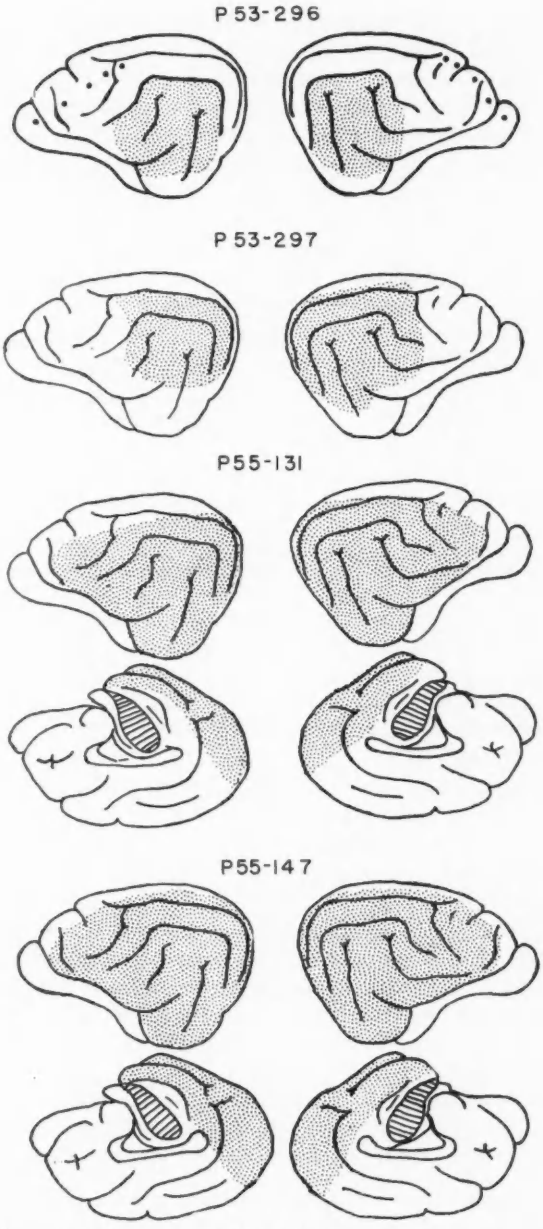

FIG. 6.—Diagrammatic representation of cortical excisions as reconstructed from serial histological sections of the cat's brain.

by movement. It seemed rather that the phenomenon was of genuine physiological significance, tending to occur at moments of extreme activation. However, it must be distinguished from habituation of the arousal reaction and probably also from the attenuation of evoked auditory potentials resulting from prolonged, continual stimulation.

There seem, then, to be three distinct phenomena whose relations to one another are quite obscure: (i) habituation of the arousal reaction; (ii) a diminution of evoked auditory potentials resulting from prolonged, continual stimulation (Hernandez-Peon and Scherrer, 1955; Galambos, Sheatz and Vernier (1956), and (iii) a diminution of evoked auditory potentials resulting from extreme activation.

Habituation after destruction of auditory cortex.—Auditory cortex continues to respond to stimuli which, through repetition, have lost their power to elicit generalized activation. This does not rule out the possibility that primary sensory cortex plays an essential role in habituation of the arousal reaction, perhaps by modulating the activity of the arousal mechanism through corticifugal pathways. We were interested, therefore, in the effects of destruction of auditory cortex on habituation to sound.

Four animals were prepared with bilateral cortical lesions. In one cat (fig. 6, 296) the lesion was restricted to auditory I and II and the posterior ectosylvian gyrus, with some extension inferiorly in the pseudosylvian region. In the second (fig. 6, 297) the lesion was extended to include most of the suprasylvian gyrus. In the third and fourth cats, the lesion was extended still further to include somatic II and all of the neocortex except gyrus proreus and a strip of cortex along the sagittal fissure (fig. 6, 131 and 147).[1]

The animals were tested at various intervals (up to four months in one case) following the cortical ablation. It should be borne in mind that our method permitted considerable variation in depth of sleep and inter-trial interval, thus making it impossible to detect small quantitative individual differences in the parameters of habituation. However, so far as could be determined within the limitations imposed by the method and the small number of subjects, the cats with extensive cortical lesions did not differ in any systematic way from normal animals in their capacity to become habituated to sounds of a specific frequency. The remarkable specificity of the habituation phenomenon even in animals with the most extensive cortical lesions is indicated in fig. 7. This cat, with bilateral lesions including auditory I and II, somatic II, suprasylvian and posterior marginal gyrii, after having become completely habituated to a 700 c/sec. tone could still be aroused by either a 200 or 1,200 c/sec. tone.

[1]Retrograde degeneration in the thalamus of these animals is being studied at present.

One cat with auditory I and II and suprasylvian gyrus destroyed (fig. 6) was also tested for the day-to-day persistence of habituation. The

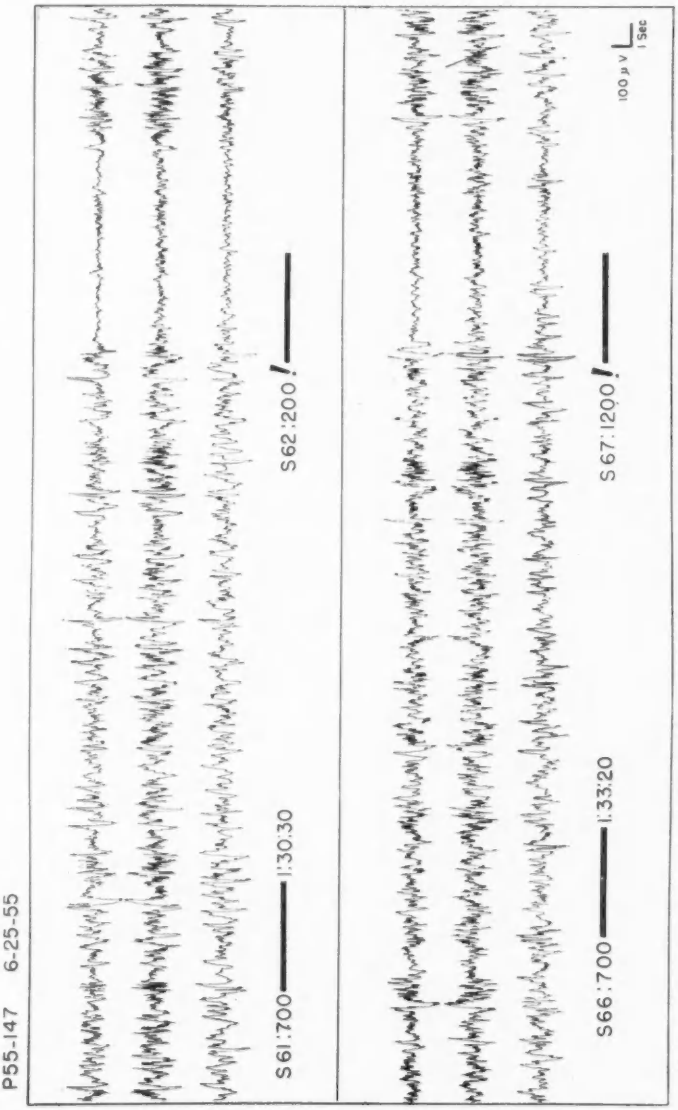

FIG. 7.—Frequency specific habituation to a 700 cycle tone in cat following large neocortical excision as shown fig. 6 (P55-147).

procedure was essentially the same as that described above (under "duration of habituation"). About ten weeks after the cortical ablation, a loud speaker was attached to the home cage, and the cat was exposed to a 500 c/sec. tone every quarter of an hour. Ten days later, electrodes were implanted, and two days were allowed to elapse during which the cat was not exposed to the stimulus. After the two-day rest period, a novel 100 c/sec. tone was more effective in producing cortical activation than the familiar 500 c/sec. tone. As in the case of the normal cat, however, the 100 c/sec. tone lost its initial advantage in a few trials.

Efforts to obtain habituation selective for the *pattern* of a given sound in animals lacking auditory cortex were generally unsuccessful. At present, it is not possible to say whether this indicates a genuine impairment of function due to the operation, or whether it was the result of chance variation, since we were not always successful in obtaining pattern-specific habituation even in intact animals.

Thus, so far as could be determined with the present method, the parameters of habituation are unchanged after extensive bilateral damage to the cortical areas subserving audition, except, possibly, the capacity of the habituation process to be selective for the pattern of a repeated sound. It is interesting to compare these results with the results of previous studies which have used the conditioned reflex method. Diamond and Neff (1953) have reported that complete ablation of electrically excitable auditory cortex does not prevent animals from acquiring conditioned differential responses to tones, although it does prevent conditioned pattern discrimination. On the other hand, according to Meyer and Woolsey (1952), if somatic II is bilaterally destroyed in addition to auditory I and II, pitch discrimination is permanently lost. In the present experiment, however, we were unable to detect any differences between animals in which only auditory I and II had been destroyed and animals in which the lesion included also somatic II.

It would appear that the relatively primitive kind of pitch discrimination observed in our experiments does not require auditory cortex even when the latter is given the most broad interpretation.

Habituation after interruption of the brain-stem auditory pathways.— In the experiments of Lindsley, Schreiner, Knowles and Magoun (1950), cats in which the auditory pathways had been severed at the level of the superior colliculi could still be aroused by intense sounds, presumably through the mediation of collateral pathways entering the reticular activating system below the collicular level. It occurred to us that considerable light might be shed on the habituation phenomenon by the study of preparations in which the primary sensory tracts had been interrupted leaving intact only the collateral pathways to the reticular system through which auditory signals could be communicated to the hemispheres.

In four animals, an attempt was made to destroy the lateral lemniscus bilaterally below the level of the inferior colliculus by passing high-frequency current through electrodes which had been introduced through the posterior fossa and oriented along the horizontal plane (H-2) of the stereotaxic instrument. In no case were the lemnisci completely severed. Even in the best preparation, it was possible to pick up some evoked potentials from one hemisphere during a terminal experiment. This animal was not somnolent, but the threshold of the arousal reaction was greatly elevated. The animal could be aroused by intense tones, however, and it became habituated to these stimuli rapidly. The habituation was specific to the frequency of the repeated sound, but it was apparently not pattern-specific.

In later experiments, we attempted to sever the somewhat more accessible brachia of the inferior colliculi. During the operation, the responses of auditory cortex to clicks were monitored on an oscilloscope, and the coagulated area was enlarged until the primary cortical responses disappeared. An example of one of these lesions is shown in fig. 8. In one of the three cats prepared in this way, some evoked potentials were subsequently obtained from the auditory area of one hemisphere.

None of the three cats was somnolent after the first few days following the operation, but the threshold of the arousal reaction to sound was greatly elevated. Tonic activation patterns could be produced fairly reliably by the use of unusually intense tones. Frequently, these activation patterns had extremely long latencies—many seconds intervening between the termination of the stimulus and the onset of cortical activation. In this connexion, we may mention the apparent *summation* over a series of arousal stimuli which often occurred in these preparations. If an ineffective arousal stimulus were repeated several times at intervals of 30 seconds or so, even though it failed completely on its first occurrence to produce any detectable alteration in the electrocorticogram, it might on its third or fourth repetition produce a full-fledged run of EEG activation.

Studies of habituation gave similar results for the three preparations. The animals became habituated very rapidly to intense tones, usually in three or four trials. The selectivity of the habituation for the frequency of the repeated stimulus was greatly impaired. In spite of many attempts, we were able to obtain evidence in only one instance of frequency-specific habituation in animals in which the brachia of the inferior colliculi had been severely damaged. In that instance, a cat which had become habituated to a 1,000 c/sec. tone could be aroused momentarily by a novel 100 c/sec. tone. Usually, once the animal had become habituated to a repeated tone, it failed to respond to all tones of the same intensity. The habituation was modality-specific, however, since it was possible to arouse the animals by near-threshold tactile stimuli after they had become completely habituated to an auditory stimulus.

The failure to observe a similar loss of specificity of the habituation phenomenon in animals with lesions below the level of the inferior colliculus was probably due to incomplete severance of the lemnisci.

Discussion

In discussing our results, we shall propose several hypotheses concerning the organization of the arousal system, and the site and nature of the changes underlying habituation. These hypotheses must be regarded as tentative, suggested but not finally proven by the available evidence.

In interpreting the present results, it is helpful to distinguish between two kinds of activation reactions. One, the "phasic" reaction, rarely outlasts the stimulus by more than 10 or 15 seconds, it has a short latency, it is very resistant to habituation, and once habituated, it recovers within a few minutes. The other, the "tonic" reaction, varies in duration from a few seconds to many minutes, it may have a remarkably long latent period (up to 30 seconds), it is labile, subject to rapid habituation, and it tends to recover slowly, over periods of hours or days.[1]

In normal animals, the two occur together and cannot be distinguished except in special circumstances—e.g. after partial habituation, when only the phasic type of reaction is elicited. However, the two types of reactions may be dissociated by brain-stem lesions. Thus, animals in which the primary sensory pathways have been severed at the collicular level so that the thalamus is deprived of direct auditory innervation are apt to exhibit long latency, tonic activation patterns which habituate extremely rapidly. On the other hand, animals in which the mesencephalic reticular system has been damaged leaving the sensory pathways to the thalamus intact exhibit only brief arousal patterns which barely outlast the stimulus (Lindsley *et al.*, 1950). Unfortunately habituation has not yet been studied in preparations of the latter type.

It will be helpful, perhaps, to distinguish between the upper and lower components of the activating system. In the present experiments, interruption of the auditory pathways (and perhaps also some adjacent portions of the brain-stem) at the collicular level seemed to prevent signals from reaching the mechanism responsible for the phasic, habituation-resistant type of reaction. Yet, bilateral destruction of auditory cortex including auditory I and II, somatic II and suprasylvian gyrus had no such effect. This suggests that direct stimulation of the upper component of the activating system from adjacent sensory structures produces the phasic type of reaction, whereas stimulation of the reticular system through collaterals in the lower brain-stem is responsible

[1]In a paper delivered at the XIV International Congress of Psychology on "Higher Nervous Activity and the Problem of Perception," E. N. Sokolov of Moscow University makes a similar distinction between two forms of the "orienting reflex."

for the tonic type of reaction. Thus, the medial geniculate bodies and closely associated structures may serve a very important function in controlling the rapid but brief alerting reactions mediated by the upper, diencephalic component of the activating system.

Another difference in the two components of the activating system appears if we consider the selectivity of the habituation process for the repeated stimulus. There is marked loss of specificity of habituation to the frequency of the repeated sound after the primary sensory tracts have been interrupted at the collicular level. Thus, habituation of the tonic reaction mediated by the reticular system is apt to be much less specific than habituation of the phasic reaction originating in the diencephalon. This is consistent with the considerable degree of convergence of afferent signals in the reticular formation (French, Verzeano and Magoun, 1953). It may also explain the tendency of long-lasting states of habituation to generalize rapidly over a wide range of stimuli, especially if the tonic reactions originating in the reticular formation recover only slowly after habituation as compared with the phasic reactions originating in the diencephalic portion of the activating system.

It is evident that if the activating system is to play an important role in the *waking* animal—alerting the central nervous system and compelling attention in the presence of novel and biologically important stimuli, it must be sensitive to slight changes in the quality of stimuli impinging on the organism's receptors. Moreover, it must be capable of producing rapid but brief shifts in the reactivity of the central nervous system. Our evidence indicates that only the diencephalic component of the activating system has these properties. The more caudally situated reticular system is capable only of crude differentiation between stimuli and produces long-lasting, persistent changes in the level of reactivity. The properties of the brain stem reticular system, therefore, are well-suited to the maintenance of wakefulness over long periods of time, but ill-adapted to the sudden and brief changes in reactivity that must occur in response to highly specific stimuli if the animal is to meet the demands of its waking environment.

What is the anatomical substrate of the important diencephalic component of the activating system? On this point, we have only presumptive evidence. According to the present conception of the organization of the activating system, it is supposed that activity initiated in the reticular formation of the mesencephalon is communicated to the cortex through both thalamic and extra-thalamic pathways (Starzl, Taylor and Magoun, 1951). The thalamic pathway has been provisionally identified with the unspecific projection system of the thalamus, first studied in the classical experiments of Morison and Dempsey (1942). There is abundant evidence that this system has physiological properties distinct from those of the lower reticular activating system. As one

example, we may mention the fact that slow, repetitive stimulation of the unspecific thalamic projection system is apt to produce recruitment, whereas slow, repetitive stimulation of the mesencephalic reticular formation produces a marked attenuation in the size of evoked potentials (Jasper, 1949; French, Verzeano and Magoun, 1953). On the other hand, rapid, repetitive stimulation of either system elicits widespread cortical activation (Morruzi and Magoun, 1949). It is possible, therefore, that the phasic reaction observed in the present experiments depended on stimulation of this unspecific thalamic projection system from the medial geniculate bodies and associated sensory structures. One of us has previously suggested that the unspecific thalamic system is strategically situated for subserving attentive processes in the conscious animal—a proposal which is consistent with the present evidence (Jasper, 1949; Adrian, Bremer and Jasper, 1954, p. 374).

What can be said about the site of the neural changes underlying habituation of the arousal reaction? In the first place, it is clear that this kind of habituation does not depend on changes occurring in the primary sensory pathways—i.e. the pathways responsible for conveying impulses to the cortical projection areas, since primary cortical responses could still be obtained from the projection areas, and indeed were somewhat larger, after the stimulus lost its power to elicit generalized activation. Nor can the change upon which habituation of the arousal reaction depends be restricted to sensory cortex, since complete removal of auditory cortex did not prevent animals from showing habituation highly selective for specific tones. This leaves the multisynaptic, extralemniscal systems—the unspecific thalamic projection system and the lower reticular activating system with their associated "collateral" pathways—as the probable site of the changes on which habituation of the arousal reaction depends.

The remarkably long latent periods occasionally observed in these experiments, especially in animals in which the primary sensory pathways had been severed at the collicular level, deserve some comment. One might suppose that an activation reaction could be initiated in the mesencephalic reticular system and could spread slowly—over many seconds—to the cortical mantle, but electrodes placed in the reticular formation in the present experiments failed to reveal any characteristic sign of activation during the latent period preceding the onset of cortical activation. This does not preclude the possibility that some form of functional activity not distinguished by an easily observable electrical sign occurs in this area during the latent period. In this connexion, it has been shown that cortical activation may be produced by adrenaline acting directly on structures in the region of the mesencephalic reticular formation (Bonvallet, Dell, and Hiebel, 1954; Dell, Bonvallet and Hugelin, 1955; Rothballer, 1955), and since adrenaline and noradrenaline

are normally present in this area in significant quantities, it has been suggested that an adrenaline-like neurohumor may act as a transmitter substance in the mesencephalic reticular system (Vogt, 1954; Dell, Bonvallet and Hugelin, 1955; Rothballer, 1955). The gradual accumulation of such a relatively stable neurohumor may account for the long-latency, tonic reactions that we have described. In an unpublished experiment, Sharpless and Rothballer (1955) were able to produce long-latency (about 30 seconds) reactions quite reliably by presenting a weak tactile stimulus to a cat in which the lateral sensory pathways in the brain stem had been severely damaged. Since the same effect could be produced with equal reliability after bilateral adrenalectomy, it was concluded that the long-latency, tonic reactions did not depend on the participation of the adrenal glands.

The present experiments shed little light on the ultimate nature of the habituation process. The longest known after-effect of stimulation in peripheral nerve is a slight lengthening of the refractory period following prolonged repetitive stimulation (von Brücke, Early and Forbes, 1941). Such effects may be more marked in the central nervous system. We know that different neural tissue is differentially susceptible to habituation. The mesencephalic reticular system with its collateral pathways must be particularly susceptible, whereas the unspecific thalamic projection system and the pathways through which it is connected with the sensory apparatus of the thalamus seem to be less susceptible. The primary sensory tracts themselves show response decrement only if the stimulus is repeated at relatively short intervals over long periods of time. It is known from studies of animal behaviour that different reflex arcs differ in their susceptibility to habituation. Monosynaptic reflexes and some polysynaptic reflexes (e.g. the pupillary reflex) show very little habituation, and of course, responses to painful stimuli tend to be resistant to habituation (Prosser and Hunter, 1936; Lehner, 1941).

In connexion with the differential susceptibility to habituation of different neural tissue, it is significant that Vogt (1954) found that drugs which stimulate the medial portion of the brain stem caused a depletion of the adrenaline and noradrenaline commonly found in this area. Prolonged electrical stimulation of preganglionic nerves produces no parallel fall in the sympathin content of the stimulated ganglia. She points out the possibility that the processes of resynthesis in the brain are less efficient in keeping up with utilization than in the periphery. Further evidence along this line may help us to understand the ultimate nature of the changes in neural functioning produced by experience.

Summary and Conclusions

Habituation of the arousal reaction, as indicated by a characteristic activation pattern in the electrical activity of the cortex, has been studied

in cats. Repetition of a specific tone, which initially produces long-lasting arousal of a sleeping cat, fails to do so after 20 or 30 trials. A study of the effect of variations of the stimulus, and the effect of cortical and subcortical lesions upon this habituation phenomenon has led to the following conclusions.

(1) Habituation of the arousal reaction is specific to the quality, modality or pattern of a given stimulus.

(2) There are two types of arousal reaction, one of short latency and brief duration, another of longer latency and greater persistence after the end of stimulation. These have been called the phasic and tonic form of reaction respectively.

(3) The long-lasting tonic reaction was most susceptible to habituation; the rapid phasic reaction was much more resistant to habituation.

(4) The electrical "activation pattern" (low voltage rapid activity) was similar in thalamus, medial brain-stem and cortex, and disappeared from all these areas with repetition of the stimulus.

(5) Habituation of the arousal reaction does not depend on changes occurring in the specific auditory system, as judged by the persistence (and even enhancement) of cortical auditory potentials with repeated stimuli which produced complete habituation of the arousal reaction.

(6) The specificity of habituation to the frequency of the repeated sound is unaffected by complete ablation of all cortical auditory receiving areas and adjacent cortical structures. Discrimination between tonal patterns, however, may be impaired by such cortical destruction.

(7) Complete section of the brachium of the inferior colliculus bilaterally raises the arousal threshold, abolishes the rapid phasic response, increases the speed of habituation and greatly impairs the tonal specificity of habituation.

(8) The tonic slow and persistent arousal response is probably mediated by the lower portions of the ascending reticular system which is capable of habituation selective for a given modality of sensory stimulation (auditory *v.* somatic) but not for more highly differentiated qualities of the stimulus.

(9) The more rapid and more highly differentiated arousal response is probably mediated by the upper portions of the activating system, particularly the unspecific thalamic projection system and adjacent sensory structures.

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We should like to express our gratitude to our many colleagues in the Montreal Neurological Institute and the Department of Psychology of McGill University for their suggestions and aid. In particular, we should like to thank Dr. Jerzy Olszewski for help in histological studies and operations, Dr. Peter Milner for valuable suggestions and for participation

in several experiments, and Dr. David Ingvar for operative and procedural help during the early phases of the study.

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LEGEND FOR PLATE

PLATE LVI

FIG. 8.—Microphotographs of lesions of the brachium of the inferior colliculus and adjacent tissue of the brain-stem in one cat (P55–55) described in text.

PLATE LVI

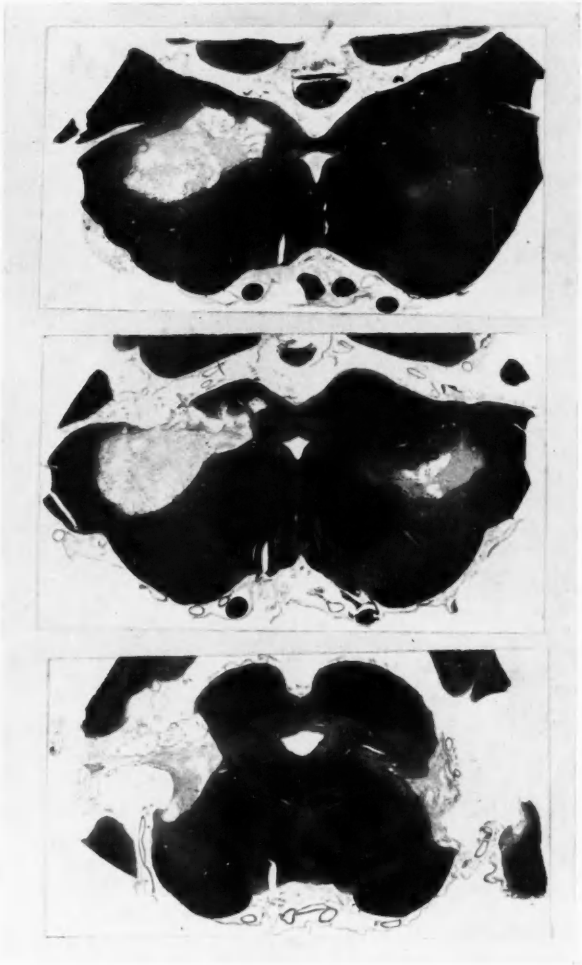

FIG. 8.

To illustrate article by Seth Sharpless and Herbert Jasper.

NOTICES OF RECENT PUBLICATIONS

ANATOMY AND LOCALIZATION

The Neuroanatomical Basis for Clinical Neurology. By TALMAGE L. PEELE, M.D., Assistant Professor of Anatomy and of Medicine, Duke University. Pp. 564. Figs. 317. London: McGraw-Hill Book Co., Inc. Price £4 14s. 0d.

The structure of many of the American teaching centres is such that it is natural for the physician or surgeon to spend much of his time in the laboratory as well as in the ward. The quantity of research work emerging from these centres is a reflection of this practice, and the quality of some of it is its justification. Another product is the highly specialized clinical worker, or the academician with clinical leanings. A result further removed is the appearance of specialized texts which link the practice of medicine to its expanding basic sciences, texts which are more natural and vital in neurology than any other branch of medicine.

Dr. Peele has in this large new textbook of neuroanatomy set a standard which will surely satisfy his anatomical colleagues, and he certainly has met a need felt by those clinical workers who are concerned for more than the routine care of patients. Though he has found it impossible to escape from the usual anatomical somatic division of the nervous system, he has modified that division upon the basis of function, and in each chapter carries the reader along through structure and normal function to a glimpse of abnormal function. He has not attempted a text of clinical neurology nor is the book in the least semiological.

Neurological anatomy is presented in such chapters as those on "The Thalamus," "The Reticular System," "The Prefrontal Cortex," "The Auditory Pathways and the Temporal Lobes," whose titles reflect the author's attempt at functional continuity. Though there is an enormous and accurate bibliography, references do not clutter the text, and they are chosen with a criticism extraordinary in such a comprehensive book.

Classical anatomy is handled succinctly, with excellent photographs and diagrams, but in such a chapter as that on the cerebellum the reader is taken to the fringe of knowledge, which is traced in the cathode ray tube as well as in silver stains. The present advance of micro-anatomy through the study of action potentials and through the functional results of ablation and stimulation is most evident.

In his chapter on the cerebellum, having dealt with the morphological studies based on Cajal's work, Dr. Peele goes on to the embryological work of Larsell, discusses electrophysiological work from McCulloch and Magouns' laboratory, the more basic experimental work of Moruzzi, and Adrian's strychnine experiments. Then we have one neurosurgeon, Walker, observing the effect of cerebellar stimulation in the cat, and another, Pool, in man. To

achieve such a synthesis of such scattered knowledge is an inestimable help, and if that were not enough, Dr. Peele concludes each of his chapters with a few paragraphs of summary.

Dealt with in this way, discussing the origins of knowledge of structure and function there is some inevitable overlap, but this really makes the readers' task more easy. This book can be heartily recommended to all clinical neurological workers either for occasional reading or for reference to contempo rary basic research.

Bing's Local Diagnosis in Neurological Diseases. Translated, Revised and Enlarged from the 14th German Edition by WEBB HAYMAKER, M.D., Professor of Neurology, Georgetown University School of Medicine. 1956. Pp. 478. Figs. 234. London: Henry Kimpton. Price £6 5s. 0d.

It is nearly half a century since the first edition of Bing's Kompendium, and fifteen years since Dr. Haymaker's first English translation. Though in his foreword Dr. Wartenburg says "Haymaker has retained the kernel of the old Bing" that kernel is now buried deep in the fruit of subsequent research. Indeed the title belittles the labour put into the task of modifying and adding to the original text, for Dr. Haymaker has in fact incorporated Bing's work into a contemporary survey of factual knowledge, rather than the converse. There are of necessity entirely new chapters, on radiology and electro-encephalography for instance, and throughout there are extensive and skilful additions to the original translation, supported by an enormous bibliography. The volume is indeed a labour of love, valuable in sustaining the influence of the European school in contemporary neurology, but having an appeal more to bibliophiles than cursory students. In England its price will further limit that appeal.

DENIS WILLIAMS.

THE ANATOMICAL BASIS OF CEREBRAL FUNCTION

The Organisation of the Cerebral Cortex. By D. A. SHOLL. 1956. Pp. 125. London: Methuen & Co. Price 18s.

Most of our basic concepts relating to mechanisms were formed, alas, in the days when a "machine" meant typically a steam engine or a watch, and our basic concepts were correspondingly limited. Only in the last few years have we begun to realize that vastly more complex forms can be both law-abiding and understandable, and we are now beginning, with some difficulty, to develop those new concepts that may gradually enable us to see in the cerebral cortex a picture more like the actual state of affairs than the utterly inadequate picture that we saw only a few years ago.

The attempt to think of the cerebral cortex on a scale adequate to the real thing can be made in many ways—by abstract statistical methods, by comparing it to a large computer, and by treating it as a transducer for the processing of information: Sholl's book takes the interesting and original method of considering the cerebral cortex first in its histology and then in the types of dynamics that the histological structure suggests. It propounds no particular or detailed solution to the problem of organization, but rather concentrates on the essential

preliminary of making clear the foundations on which any solution, if it is to be valid, must rest. It gives a scholarly and readable account of these foundations, and gives many reasons for thinking that the basic concepts in which the problems of organization will eventually be solved are statistical.

W. ROSS ASHBY.

REGENERATION IN THE NERVOUS SYSTEM

Regeneration in the Central Nervous System. By 33 contributors. Edited by WILLIAM F. WINDLE, Foreword by PEARCE BAILEY. Pp. 311. Figs. 62. Springfield, Illinois, U.S.A.: Charles C. Thomas. Price £3 9s. 0d.

This is a monograph fashioned from a series of papers which were read and discussed at a Conference in May 1954, at Bethesda, Maryland, U.S.A. The Chairman of the Conference (which was sponsored by the National Advisory Neurological Diseases and Blindness Council of America) was Louis B. Flexner. It contains a series of contributions of various lengths from no less than thirty-three persons, each of whom is an acknowledged expert in his field. The authors represent disciplines which range from biochemistry through psycho-biology, anatomy, physiology, pharmacology and pathology to clinical medicine. The editor has skilfully linked the papers by the insertion at appropriate places of abstracts of the discussions which took place. He has also added comments and relevant material omitted by those contributing to the Conference in the form of footnotes. The editor is also responsible for an integrated and exhaustive bibliography in which the full title of each work is included.

The monograph is so well edited that it might be taken for an interim report from an operational research group with a single over-all objective framed by the question: "Is structural regeneration and restitution of function possible in man following complete interruption of the processes of neurons intrinsic to the central nervous system?"

As Pearce Bailey points out in a foreword to the monograph, a firm, obligatory and almost canonical slogan that regeneration does not occur in the central nervous system has prevailed in neurological education for almost half a century and has engendered a feeling that some negative law of nature forbids regeneration. Convictions of this kind are notoriously difficult to eradicate, for contrary evidence tends to be either overlooked or ignored, particularly if it appears in the form of highly technical articles isolated within a diversity of disciplines. The particular value of this monograph is that such papers do not stand in isolation. Each has been so placed in relation to its neighbours that it plays a part in the emergence of a series of observations which give a new insight and point the way to further research into the many factors which contribute to the potentiality for regeneration of neurons intrinsic to the central nervous system.

The observations reported in this monograph dispel any notion that regeneration of neurons intrinsic to the central nervous system is impossible. Indeed, there is unequivocal evidence that structural regeneration with useful

functional restitution can take place following transection of the spinal cord in amphibia. Moreover, structural regeneration can and under certain circumstances (particularly under the influence of Piromen) does occur in the mammalian central nervous system. However, no one has yet presented an unequivocal demonstration that useful functional restitution can take place in this species.

This is both a valuable and stimulating book and should be read by everyone interested in any aspect of neurology. Its value rests not only upon the factual information which it contains but upon its revelation of the potential value of operational research in neurology.

The book is beautifully produced but somewhat surprisingly there are a few obvious typographical spelling mistakes. Fortunately none of them is misleading.

GRAHAM WEDDELL.

THE CEREBROSPINAL FLUID

Physiology of the Ocular and Cerebrospinal Fluids. By HUGH DAVSON. 1956. Pp. 388. Illustrations 109. London: J. & A. Churchill Ltd. Price 65s.

A new book on the physiology of the cerebrospinal fluid is very welcome for it is some time since the very large volume of relevant literature on this subject has been reviewed. There is obviously an advantage in discussing the aqueous fluid alongside the cerebrospinal fluid as these two fluids have much in common.

The book is composed of chapters dealing chiefly with morphology, with chemical composition, with the various blood-fluid barriers and with problems of fluid pressure. Physiological functions are almost solely discussed by the author, who is a well-known experimenter more especially on the aqueous fluid. Unfortunately from the point of view of clinician and pathologist disease processes are only very rarely mentioned, and then only in so far as they affect physiology, but the neurologist will do well to study the pages devoted to the cerebrospinal fluid.

The results of a very large number of workers are discussed, but this at times leaves the reader without a clear idea of the value of the work cited, and there could with advantage be a short summary at the end of each chapter, which would enable one to obtain a composite view of the problem.

One irritating feature is the large number of footnotes, most of which could either have been included in the text or else omitted.

Despite these criticisms the book is well written, it is quite readable and covers the field very adequately, and it is obvious that every research worker in each of these fields will need to have this volume on his library shelf.

The publishers and the author must be congratulated on producing a book in which errors do not appear to have crept into the text, and in which the illustrations do demonstrate the points discussed.

J. N. CUMINGS.

PHILOSOPHICAL ASPECTS OF NEUROLOGY

Analysis of Perception. By J. R. SMYTHIES, M.A., M.D.Cantab., M.Sc.Brit.Col., D.P.M.Lond. 1956. Pp. 140. Preface by Sir RUSSELL BRAIN, Bt., D.M., LL.D., D.C.L., P.R.C.P. International Library of Psychology, Philosophy and Scientific Method. London: Routledge and Kegan Paul. Price 21s.

Dr. Smythies has already published a number of original papers on the philosophical and neurological problems associated with the word "perception." Now, after several years of special training in departments widely scattered in their interests and geographical location, he has produced a book the main value of which will be to force philosophers to acquaint themselves with the facts of neurology, clinical psychiatry and psychology. At the same time he provides an opportunity for neurologists to acquaint themselves with the philosophical and linguistic theories which have such an important and fashionable place in contemporary thought. Though Dr. Smythies has done everything possible to equip himself for his task of synthesis, there must be points in the various fields of study that will provide material for criticism by experts. In discussing the statement that "vision works like television" (with only a footnote elsewhere to say that television should be considered as working like vision—a point of the greatest importance to his whole theory) it is assumed that there is such a process as vision with which the child is endowed. Because the adult can recognize a giraffe from a picture of one, it is supposed that a child seeing the world only by means of a television screen and camera as his visual apparatus, would have the same knowledge by visual means, "in spite of the fact that it would have no 'direct' knowledge of any physical object except the screen of the television set before its eyes." He forgets that what we call "vision" is a complex derived from total nervous activity, including in particular all the sensations derived from the vestibular and locomotor apparatus. Vision is not a photographic process. Vision includes the awareness and knowledge of all aspects of the subject, but the screen or photograph is composed of a two-dimensional surface, blank on the back. This error at the base weakens the readers confidence in the stability of the superstructure.

Being opposed to words such as "sound," or "colour-patch," Dr. Smythies defines "*sense-datum*" in terms of the after-image derived from an electric light bulb in four different ways of varying complexity, the fourth of which reads as follows:

> "Definition 1.4. 'IF the boundary J' of x forms a Jordan curve which decomposes $y = x - J'$ into two regions whose common boundary is J', then x is a sense-datum'."

The complexity of such statements, apart from their acceptance, makes the work difficult to read sympathetically, and it is to be feared that the book will not reach the scientific conscience of enough readers. Those, however, who find themselves avoiding the exercise of concentration and criticism necessary to assess this bravely original and learned book, should feel that possibly they may be likened to Moses, viewing a "promised land," close to which his leadership had brought him, but which he was destined not to enter nor to cultivate.

Physics Psychology and Medicine. By Professor J. H. WOODGER, D.Sc. 1956. Pp. 146. London: Cambridge University Press. Price 8s. 6d.

This "somewhat complicated" but charmingly written essay is directed towards a change of policy in medical education. Considering the prevalence of mental illness, the brief and late attention to psychology in the training of doctors is criticized. The "lopsidedness" is shown to be due to the prestige of physics which seeks to reject personal relationships in its own sphere The author feels that each science should be autonomous, developing its own new and special methods. He gives examples of the linguistic approach for which he is so well known.

The suggestions will create opposition because of their fundamental and original nature, but neurologists and others should not shut their eyes to the altering structure of scientific thought.

WILLIAM GOODDY.

THE NEUROSES

The Neuroses in Clinical Practice. By HENRY P. LAUGHLIN. 1956. Pp. xlii + 802. Philadelphia and London: W. B. Saunders Company. Price 87s. 6d.

This is a large-scale systematic textbook of the neuroses, based on an exclusively psychogenic ætiology and a formulation in terms of mental mechanisms. The mental mechanisms, which may be of many kinds, conversion, depressive, obsessive-compulsive, etc., are in large part to be taken as methods of defence by the individual to the occurrence of anxiety, which is thus made the central ætiological factor. The approach is an interesting one; but its one-sidedness in ignoring a great range of observations which do not fit in with the central hypothesis greatly depreciates its scientific value.

ELIOT SLATER.

THE FIRST INTERNATIONAL CONGRESS OF NEUROLOGICAL SCIENCES

will be held in Brussels from Sunday, July 21, *to July* 28, 1957

This comprises the:

6th International Congress of Neurology.
1st International Congress of Neurological Surgery
3rd International Congress of Neuropathology.
4th International Congress of EEG. and the Clinical Neurophysiology.
5th Symposium Neuroradiologicum, and the
5th Meeting of the International League against Epilepsy.

The main topics set down for discussion at the Congress are as follows:

Symposia: Extrapyramidal Disease

Symposia: Significance and Interpretation of Modifications of Consciousness.

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